The effect of physiotherapy on respiratory function in ventilated children

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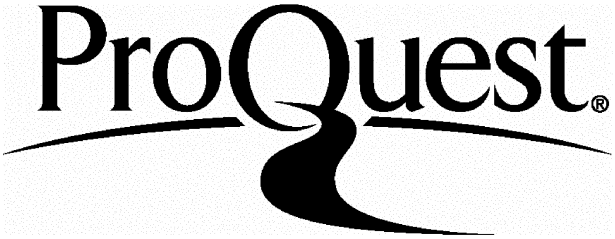

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Abstract

Background: Chest physiotherapy to clear secretions is routine in many intensive care units, although there is little evidence to substantiate its use above routine suction procedures. Until recently evaluation of such treatments has been limited by a lack of objective measures of respiratory function. This study aimed to evaluate the performance of a new respiratory function monitor in assessing the effects of therapeutic interventions such as physiotherapy. In addition the study aimed to establish whether physiotherapy offered an advantage over routine suction procedures with respect to selected indices of respiratory function.

Subjects: Consent was obtained for 101 muscle relaxed, fully ventilated children recruited to the study between April 1998 and March 2000. Of these, 56 had a primary cardiac diagnosis and 45 had primary or secondary respiratory problems and all required physiotherapy treatment.

Methodology and equipment: Validation and pilot studies were undertaken to assess the accuracy of the "CO_2SMO Plus". Subjects were randomly allocated to receive either physiotherapy or nursing suction in the morning and the alternative intervention in the afternoon. Arterial blood gases, tidal volume, respiratory mechanics, CO_2 parameters and deadspace values were recorded before and after both interventions. Group and individual responses to treatment were evaluated and compared.

Results: Validation studies demonstrated that the "CO_2SMO Plus" could provide accurate and reproducible data, provided that tracheal tube leak was <20%. Data from 89 children (tracheal tube leak <20%) were analysed, 81 of whom had both physiotherapy and nursing suction performed on the same day. Physiotherapy treatments were significantly longer than nursing suction, involved greater saline instillations and more suction catheters ($p<0.005$). Physiotherapy resulted in increased alveolar and physiological deadspace ($p<0.01$) and reductions in R_{rs}, HCO_3-, base excess, O_2 saturation and $PeCO_2$ ($p<0.05$). Following nursing suction, V_{TE} and C_{rs} were reduced ($p<0.05$). There was considerable individual variation in response to both physiotherapy and suction.

Conclusions: The "CO_2SMO Plus" was accurate and useful for investigating the effect of clinical interventions in muscle relaxed patients, provided that tracheal tube leak was <20%. The demonstrable differences between the physiological effects of physiotherapy and nursing suction could be attributable to the longer, more vigorous physiotherapy treatments which included chest wall vibrations.

For my father, who started out on this project with me,
but then departed this world to do a higher degree of his own, with love always.

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"Beware of the man who works hard to learn something, learns it, and finds himself no wiser than before. He is full of murderous resentment of people who are ignorant without having come by their ignorance the hard way."

Kurt Vonnegut, Jr. - Cat's Cradle

Project Supervisors:

Professor Janet Stocks: Institute of Child Health, London

Professor Di Newham: Kings College, London

This project was granted approval by the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust Research Ethics Committee and written, informed consent was obtained from parents of infants and children who were recruited into the study.

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List Of Abbreviations and Definitions

Abbreviation	*Definitions and Units*
abg	arterial blood gas
ASD	atrial septal defect
ARDS	acute respiratory distress syndrome
AVSD	atrio-ventricular septal defect
BE	base excess
BPD	bronchopulmonary dysplasia
BTPS	body temperature, barometric pressure and water vapour saturated conditions
CICU	cardiac intensive care unit
CO_2	carbon dioxide
CPAP	continuous positive airways pressure, cmH_2O, kPa ($1cmH_2O$ = 0.098 kPa)
C	compliance, mL/cmH_2O or L/kPa, ($1mL/cmH_2O$ = 10.2 mL/kPa)
C_{rs}	respiratory system compliance: the distensibility of the respiratory system mL/cmH_2O or L/kPa (may be expressed per kg body weight). $1mL/cmH_2O$ = 10.2 mL/kPa
CV	coefficient of variation, %, CV = (SD/mean) X 100
ds	deadspace, mL/kg
E	elastance (the reciprocal of compliance) cmH_2O/mL
ECMO	extra-corporeal membrane oxygenation
$ETCO_2$	end tidal CO_2, kPa
F	gas flow
FEV_1	forced expiratory volume in one second
FiO_2	fractional oxygen concentration of inspired gas
FRC	functional residual capacity
GLM	general linear model
HCO_3-	bicarbonate, abundant buffer in blood plasma, regulated by kidneys
ICU	intensive care unit
IVH	intra-ventricular haemorrhage
kg	kilogram
LA	limits of agreement (mean difference +/- 2 SD)
MAP	mean airway pressure, cmH_2O or kPa, ($1cmH_2O$ = 0.098 kPa)
N_2	nitrogen gas
NS	non significant
P	pressure
PaO_2	partial pressure of O_2 in arterial blood, kPa
$PaCO_2$	partial pressure of CO_2 in arterial blood, kPa
PAO_2	partial pressure of O_2 in alveoli, kPa
PCV	pressure controlled ventilation

Abbreviations and Definitions continued...

Abbreviation	*Definitions and Units*
$PeCO_2$	mixed expired CO_2, kPa
PEEP	positive end expiratory pressure, cmH_2O or kPa ($1cmH_2O$ = 0.098 kPa)
PEF	peak expiratory flow, mL/s
pH	measure of the balance between acids and bases in the blood plasma
Physio	physiotherapy
PICU	paediatric intensive care unit
PIE	pulmonary interstitial emphysema
PIP	peak inspiratory pressure, cmH_2O, kPa ($1cmH_2O$ = 0.098 kPa)
PRVC	pressure regulated volume controlled
R	resistance
R_{app}	resistance due to apparatus, $cmH_2O/L/s$ or kPa/L/s, ($1cmH_2O/L/s$ = 0.098kPa/L/s)
Resp. rate	respiratory rate, breaths/minute
R_{rs}	total respiratory system resistance, $cmH_2O/L/s$ or kPa/L/s, ($1cmH_2O/L/s$ = 0.098kPa/L/s)
R_{TT}	resistance due to tracheal tube, $cmH_2O/L/s$ or kPa/L/s ($1cmH_2O/L/s$ = 0.098kPa/L/s)
SaO_2	saturation of oxygen in arterial blood, %
$SBCO_2$	single breath CO_2
SD	standard deviation
t_E	expiratory time, seconds
t_I	inspiratory time, seconds
t_{rs}	respiratory time constant, seconds
Truncus A	truncus arteriosus
Tube leak	tracheal tube leak, %, tracheal tube leak = $(V_{TI}-V_{TE})/V_{TI}$ x 100
V	volume
V/Q ratio	ratio of pulmonary ventilation to pulmonary perfusion
VCO_2	volume of CO_2 expired in mL/min (expressed per kg of body weight)
VCV	volume controlled ventilation
$V_{Dairway}$	airway deadspace, mL
V_{Dalv}	alveolar deadspace, mL
VD_{phys}	physiological deadspace, mL
VD_{phys}/ V_T	ratio of physiological deadspace to tidal volume
VO_2	oxygen consumption
V_T	tidal volume, mL
V_{TE}	expired tidal volume, mL
V_{TI}	inspired tidal volume, mL
weight	body mass, kg

1. Introduction and literature review

1.1 Introduction

Chest physiotherapy and tracheal suction to clear pulmonary secretions from the ventilated child are routine in many intensive care units. Historically, studies to assess the clinical effectiveness of such treatments have been limited by the lack of objective, non-invasive measures of respiratory function. There is little firm evidence to substantiate the use of physiotherapy in ventilated children or to recommend it above the suction techniques used by nursing staff. This study aimed to use a new portable non-invasive respiratory monitor ("CO_2SMO Plus", Novametrix Medical Systems Inc. version 3.0, CT, USA) to measure respiratory function before and after physiotherapy and nursing suction procedures. The principal aims of the study were to assess the effects of respiratory physiotherapy treatments in ventilated children and to establish whether such treatments offer a significant advantage over routine suction used by nursing staff in the intensive care unit. In addition, considerable efforts were made to validate the "CO_2SMO Plus" respiratory monitor and to evaluate its clinical usefulness in objectively assessing therapeutic interventions in the intensive care unit.

The first three chapters of this thesis include a literature review, the theoretical background pertaining to respiratory parameters of interest in this project and how they were measured or calculated by the monitor and a description of the validation work undertaken to evaluate the performance of the "CO_2SMO Plus".

The latter four chapters include a description of the study design and methodology used in the project, a report of the *in-vivo* and pilot studies performed, results of the study and a discussion of the findings with reference to other publications in relevant research fields.

Finally two publications which issued directly or indirectly from the work done in this project are included preceding the Appendix and reference list.

1.2 Literature review

Mechanically ventilated patients are inefficient at clearing mucus from their own airways. The tracheal tube covers normal ciliated tracheal tissue and prevents normal movement of mucus towards the epiglottis and oesophagus. In addition the "foreign" tracheal tube moves against and irritates the soft membranes of the tracheal walls,

thereby stimulating further production of mucus. Most mechanically ventilated infants are well sedated and may be pharmacologically paralysed, so that the ability to cough effectively is either seriously compromised or absent. Accumulation of mucus in the airways because of increased production or decreased clearance due to defects in the ciliary clearance apparatus will contribute to the morbidity of airway diseases by predisposing patients to respiratory infections, airflow obstruction and discomfort. There is a significant association between chronic production of mucus and an increased risk of mortality (Kim, 1997). The management of mucus hypersecretion can be undertaken either by improving clearance by physical methods or by pharmacological methods (Marriott, 1981; Kim, 1997). Mucus hypersecretion may not be the primary problem in many ventilated children, but the presence of the tracheal tube, as well as respiratory pathology and sedation or muscle relaxation, will significantly reduce normal mucociliary clearance, thereby creating a vulnerability to further disease. Regular suction (performed by nursing staff or physiotherapists) combined with a number of other modalities has become an important part of reducing respiratory complications associated with mechanical ventilation.

Physiotherapy techniques in intensive care have developed over the last two decades but there remains little conclusive evidence to support or guide airway clearance techniques in ventilated children. Current practice is often based on locally established routines, experience, clinical intuition based on anatomical and physiological knowledge and some wisdom from eclectic and often conflicting publications. There is also wide variability in the role of the physiotherapist in intensive care units depending on the country, training, local traditions, staffing levels and expertise. There is little, if any, evidence to recommend dynamic physiotherapy airway clearance techniques above the use of routine airway clearance techniques employed by nursing staff in paediatric intensive care units (Stiller, 2000).

The lack of research evidence to support physiotherapy practice in intensive care has also been in part due to the difficulty in identifying appropriate and sensitive outcome parameters. Until recently, equipment for measuring lung function in the intensive care unit has been too cumbersome, invasive, inaccurate or expensive to use routinely. However new developments in ventilator design and respiratory monitors have made

continuous and non-invasive measures of various respiratory parameters possible. Some of these have the potential to be useful in evaluating the efficacy of airway clearance techniques.

1.2.1 Adverse effects of mechanical ventilation

The various cardio-respiratory complications associated with mechanical ventilation have been extensively studied. They include atelectasis, barotrauma, pulmonary oedema, tracheal tube obstruction, compromised cardiac output and pulmonary blood flow, hypoxia, hypo- or hyper-capnia and nosocomial pneumonia (Rivera and Tibballs, 1992; Clough et al. 1994; Meade et al. 1997; McGuire et al. 1997; Gannon et al. 1998; Dreyfuss and Saumon, 1998; Stewart et al. 1998). Mechanical ventilation in preterm infants has been associated with retinopathy of prematurity, intraventricular haemorrhage, and bronchopulmonary dysplasia (Greenough, 1999). It has also been shown to reduce postnatal alveolar multiplication and increase the amount of bronchial smooth muscle and submucosal glands (Greenough, 1992; Thompson et al. 1992). The pathology that precipitated the need for assisted ventilation may be exacerbated by the high tidal volumes or airway pressures needed to obtain or maintain optimal gas exchange (Parker et al. 1990; Dreyfuss and Saumon, 1993; Rosen et al. 1993).

There are few controlled paediatric studies comparing the various modes of ventilation in terms of patient outcomes. Currently, the choice of ventilator mode depends largely on the equipment available, the patient's disease state, and the clinician's preference based on personal experience (MacDonald and Johnson, 1996). Survival of small infants has improved significantly in recent years and the focus is now on reducing the incidence of ventilation-induced lung injury and other complications. This involves improved understanding of conditions producing respiratory failure, the response of the respiratory system to various therapies and the effects of changes in ventilator strategies (Stenson et al. 1998).

The rationale for physiotherapy assumes that removal of secretions from the airways will improve delivery of gas from the ventilator, help to resolve atelectasis and improve respiratory function. The improvement in clinical status may facilitate early weaning

from ventilation and reduce lung damage associated with mechanical ventilation. Preterm infants are particularly susceptible to lung damage from mechanical ventilation and should be weaned as soon as possible (Hislop et al. 1987; Haworth et al. 1989).

1.2.2 The general effects of physiotherapy or nursing suction

There are a large number of publications which are relevant to the efficacy of physiotherapy or nursing suction procedures, but many of them have significant flaws in design or execution and results have to be interpreted with caution. Published reviews examining the efficacy of respiratory physiotherapy have been frustrated by studies of poor quality or with small study numbers, multiple treatment modalities and inter and intra-professional differences in performing techniques, multiple patient groups with different diagnoses, and multiple outcomes (Hussey, 1992). The lack of consensus and conflicting results in the literature regarding optimal methods of airway clearance diminish confidence in the interpretation of research findings and extrapolation of adult studies or those in non-ventilated or selective paediatric populations to the general paediatric population. Despite quite extensive bibliographies, reviews on the efficacy of respiratory physiotherapy tend to arrive at similar conclusions: that the evidence is limited and that there is an urgent need for further research to be performed (Stiller, 2000). Sometimes airway clearance procedures are performed by nurses but referred to as "chest physiotherapy" (Dulock, 1991; Lewis et al. 1992). Unfortunately these publications have the potential to reflect inaccurately upon the practices of physiotherapists (Higgins, 1974; Ciesla, 1996; Krause and Hoehn, 2000; Flenady and Gray, 2000; van der Schans et al. 2000).

The rationale for chest physical therapy in intensive care units is to minimise pulmonary secretion retention and to maximise oxygenation by re-expanding atelectatic lung segments (Ciesla, 1996). Chest physiotherapy is regularly performed in ventilated children with the justification that it helps prevent or resolve complications associated with artificial respiration (retention of secretions and atelectasis) and speeds up the resolution of primary respiratory disorders. Prior to accessible measures of respiratory function in the intensive care unit, physiotherapists have had to rely on sub-optimal and relatively subjective markers to evaluate the efficacy of treatment. These markers have included sputum weight, changes in chest radiographs, auscultation and O_2 saturation.

Arterial blood gas measurements remain the gold standard for clinical assessment of lung function, but are not always readily available and are not necessarily routinely taken before and after chest physiotherapy.

1.2.2.1 Sputum clearance

The efficacy of sputum clearance may be demonstrated directly by sputum weight or via indirect measures of pulmonary function such as radio-labelled aerosol clearance (Bateman et al. 1981). Sputum weight has always been a controversial outcome measure in physiotherapy trials because of intra- and inter-subject variability. Sputum yield varies during the course of the day in any individual and different pathophysiology will result in different amounts of sputum but not in a predictable or consistent fashion. Some studies dispute the correlation between the amount of sputum and improved pulmonary function in ventilated patients (Mackenzie et al. 1989; Hasani et al. 1994) while others suggest that sputum clearance is associated with an improvement in respiratory function (Cochrane et al. 1977). Some authors suggest that the connection between sputum production and pulmonary function is irrelevant as long as it can be demonstrated that physiotherapy treatments are advantageous in clearing secretions (Etches and Scott, 1978; May and Munt, 1979; Pavia, 1990; Gallon, 1991). Many studies to date which used sputum weight as an outcome have been undertaken in non-ventilated patients, but a recent study found that total static respiratory system compliance (C_{rs}) and sputum clearance were improved by the addition of manual hyperinflation to a physiotherapy treatment of positioning and suctioning in mechanically ventilated patients without compromise of cardiovascular stability or gas exchange (Hodgson et al. 2000).

1.2.2.2 Arterial blood gases

The reported effects of physiotherapy treatments on arterial blood gases are conflicting. Some publications report a significant fall in PaO_2 after physiotherapy techniques or tracheal tube suction (Gormezano and Branthwaite, 1972) while others report no changes in PaO_2 after physiotherapy despite treatment protocols without pre-oxygenation (Mackenzie et al. 1978). Hypoxaemia has frequently been reported following tracheal tube suction in ventilated neonates (Holloway et al. 1966; Simbruner et al. 1981; Fox et al. 1978; Durand et al. 1989; Hussey, 1992), although Finer and Boyd showed a greater increase in PaO_2 in neonates following physiotherapy and suction than in neonates treated with postural drainage and suction alone (Finer and

Boyd, 1978). One study reported significant increases in PaO_2 after percussion in premature babies, but the study design included increasing ventilation pressures by 25%. There can be little doubt that the increase in peak inspiratory pressure is very likely to have influenced the observed improvement in blood gases after suction (Tudehope and Bagley, 1980).

Several studies in ventilated adults or infants have shown that pre-oxygenation, delivered manually or by the ventilator, completely prevented post suction hypoxaemia or produced an increase in PaO_2 immediately after treatment (Connors et al. 1980; Goodnough, 1985; Preusser et al. 1988; Kerem et al. 1990; Stone et al. 1991). Some authors suggest that in the presence of significant atelectasis, an increase in PaO_2 may be seen after resolution of atelectasis with physiotherapy, even if pre-oxygenation is not incorporated (Holody and Goldberg, 1981; Mackenzie and Shin, 1985; Ciesla, 1996). Atelectasis may be associated with more widespread disturbances of gas exchange than is generally realised, perhaps because of distension of adjacent lung regions (Fletcher and Larsson, 1985).

In summary, it appears that hypoxaemia may be associated with physiotherapy and / or tracheal tube suction. Many publications have recommended pre-oxygenation or hyperinflation breaths as effective ways of avoiding or minimising the hazards of suction and physiotherapy (Young, (a) 1984; Riegel and Forshee, 1985; Gunderson et al. 1986; Kerem et al. 1990; Shah et al. 1992; Mancinelli-Van and Beck, 1992; Odell et al. 1993; Wood, 1998). Alternatively, suction through closed ports to maintain PEEP and tidal volumes during the procedure may reduce suction related hypoxaemia (Gunderson et al. 1986).

1.2.2.3 Respiratory mechanics (C_{rs} and R_{rs})

The evidence for the effects of physiotherapy on respiratory system compliance (C_{rs}) and resistance (R_{rs}) in ventilated adults and children is also conflicting. This may be related to institutional differences in treatment modalities, differences in patient populations or differences in calculating respiratory mechanics. Suction has been associated with significant deterioration in C_{rs} in fully ventilated, muscle relaxed, new-born babies (Brandstater and Muallem, 1969) and percussion in fully ventilated adults produced a

reduction in C_{rs} after treatment, while manual hyperinflation improved C_{rs} by a maximum of 16% which was sustained for more than an hour in patients with lung disease (Jones et al. 1992). Another study found no significant difference in C_{rs} between mechanically ventilated adults who received pre-oxygenation and tracheal tube suction, with and without manual hyperinflation and chest wall vibrations after cardiac surgery (Eales et al. 1995). By contrast, Mackenzie et al, in two separate studies, found statistically significant ($p<0.01$) increases in C_{rs} 2 hours after physiotherapy in mechanically ventilated adults but no change in R_{rs} (Mackenzie et al. 1980; Mackenzie and Shin, 1985). Other studies have also shown an increase in C_{rs} after physiotherapy (Winning et al. 1975). In animal studies, negative pressure applied to the trachea was shown to decrease lung compliance and this was partly attributed to collapse of alveoli and increased venous admixture, possibly as a result of the continued perfusion of the collapsed alveoli (Velasquez and Farhi, 1964).

Very significant falls in both R_{rs} and expiratory time constant (t_{rs}) measurements have been reported after tracheobronchial suction or lavage for infants whose pre-treatment values of resistance were elevated compared with reference data. No changes in C_{rs} values were noted (Prendiville et al. 1986). In the same study, severe but clinically inapparent mucus obstruction of the airways was revealed in two infants by a progressively rising R_{rs} during continuous monitoring. In addition, R_{rs} has been shown to fall significantly ($p<0.005$) following vibrations and suction in a neonatal population, possibly as a result of the removal of secretions from the airways, but R_{rs} returned to baseline values within 2 hours of suction, (Fox et al. 1978). In non-intubated adults, significant reduction in airflow obstruction after chest physiotherapy has been reported (Cochrane et al. 1977).

1.2.2.4 Acute lobar atelectasis and chest radiograph

Atelectasis at a macroscopic or microscopic level refers to the collapse of lung regions as gases are resorbed from underventilated alveoli. Atelectasis may be due to several factors including regional airway obstruction by retained secretions. Of all the pulmonary complications associated with ventilation (including pneumonia, bronchopulmonary infection, acute respiratory distress syndrome, atelectasis and acute

or chronic respiratory disease) acute lobar atelectasis has quite consistently been shown to respond favourably to physiotherapy (Marini et al. 1979; Hammon and Martin, 1981; Fourrier et al. 1994). However, with the exception of one study (Galvis et al. 1994), most of these studies were performed on ventilated adult patients and results may not be extrapolated to a paediatric population with confidence. The predominance of upper lobe collapse observed in paediatric intensive care patients contrasts with the high incidence of lower lobe collapse in their adult counterparts. Multiple factors are likely to be contributory and include the anatomical and physiological differences between adults and children, the pathophysiology of childhood respiratory disease and more critical positioning of tracheal tubes in younger patients and their movement with patient positioning (Thomas et al. 1999).

Three randomised studies comparing the efficacy of fiberoptic bronchoscopy to respiratory therapy in resolving acute lobar atelectasis, found respiratory therapy alone to be superior or equivalent to fiberoptic bronchoscopy (Marini et al. 1979; Hammon and Martin, 1981; Fourrier et al. 1994). A further study concluded that routine post-lobectomy bronchoscopy offered no advantage over physiotherapy in preventing the development of postoperative atelectasis (Jaworski et al. 1988). Ciesla et al, in two separate studies, found that physiotherapy assisted in the resolution of atelectasis in ventilated adults and improved PaO_2 without the negative haemodynamic side effects of therapeutic bronchoscopy (Ciesla et al. 1981; Ciesla, 1996). Physiotherapy techniques in addition to hyperinflation and suction have been shown to enhance and hasten resolution of acute lobar atelectasis after a single treatment (Stiller et al. 1990; Stiller et al. 1996).

In a prospective study of 47 ventilated adults, Mackenzie et al. found that chest radiographs within 24 hours of physiotherapy showed improvement in 68% of patients. Chest physiotherapy was most effective in the treatment of unilobar densities and produced dramatic improvement in atelectasis of acute onset (Mackenzie et al. 1978).

The single paediatric study on mechanically ventilated infants, found that physiotherapy was effective in the treatment of various degrees of lung collapse. Lung expansion, documented by chest radiographs, improved notably in 48 of 57 infants (Galvis et al.

1994). Zach et al reported improvement in atelectasis in unventilated children receiving physiotherapy (Zach and Oberwaldner, 1987).

In contrast to the studies reported above, Reines et al. found that chest physiotherapy was associated with significantly ($p< 0.01$) more frequent and severe atelectasis in children after heart surgery than in patients who had not received physiotherapy (Reines et al. 1982). However, this study was done almost 20 years ago, and relatively small subjects numbers (19 and 25 in each group), coupled with the fact that both physiotherapy and ventilation techniques have evolved considerably since then, reduce the confidence with which this evidence can be applied.

1.2.2.5 Prevention and treatment of pneumonia or common pulmonary complications

Two very early publications suggested that prophylactic chest physiotherapy could prevent post-operative pulmonary complications (including atelectasis and pneumonia) in adults following abdominal surgery (Thoren, 1954; Palmer and Sellick, 1953). Since then however, there has been little consistency in the literature regarding the role of physiotherapy in prevention or treatment of common pulmonary complications in ventilated patients (with the exception of acute lobar atelectasis). While some studies suggest there is moderate evidence that routine prophylactic postoperative chest physiotherapy in both adult and paediatric populations significantly reduced the frequency of post operative complications (Bartlett et al. 1973; Morran et al. 1983; Rockwell and Campbell, 1976; Rello et al. 1996), others have reported detrimental effects or no effect in reducing the incidence or resolution of nosocomial pneumonia (Graham and Bradley, 1978; Reines et al. 1982; Ntoumenopoulos et al. 1998). One randomised trial involving 171 patients concluded that chest physiotherapy was "at best useless in patients with primary infectious pneumonia" (Britton et al. 1985).

Some authors have suggested that relatively recent policies of encouraging early mobilisation and ambulation following many surgical procedures have reduced the need for prophylactic physiotherapy treatment (Dull and Dull, 1983; Hallbook et al. 1984; Jenkins et al. 1989).

A recent Cochrane review based on three small trials found there was no evidence that peri-extubation physiotherapy compared with non-active techniques (positioning and suction alone) or no intervention prevented post-extubation lobar collapse, though there appeared to be a reduction in re-intubation episodes when 1 to 2 hourly physiotherapy treatments were performed prior to extubation (Flenady and Gray, 2000). The numbers of babies studied were small and 2 of the 3 studies were carried out over 10 and 20 years ago respectively. Since then, enormous changes have occurred both in the medical and physiotherapy management of ventilated patients. Extrapolation of this information to current practice must therefore be very guarded.

1.2.2.6 Deadspace and ventilation / perfusion balance

Very few studies have reported deadspace or ventilation / perfusion matching as outcomes for physiotherapy, although a major cause of impaired gas exchange in ventilated patients is atelectasis, causing intrapulmonary shunt. The effect of body position on ventilation / perfusion relationships has frequently been examined but this has been particularly in relation to optimising positioning in acute respiratory distress syndrome (ARDS) or unilateral lung disease, rather than specifically with regard to physiotherapy (Rattenborg and Holaday, 1967; Secker-Walker et al. 1975; Moran et al. 1977; Batra et al. 1981; Dean, 1985; McCarthy, 1987; Moriya et al. 1987; Cohen, 1997; Walther et al. 1998). A single case study reported that alveolar deadspace ($V_{D_{alv}}$) was significantly reduced after resolution of a partially atelectatic lung (Fletcher and Larsson, 1985).

Another study concluded that external mechanical vibration of the chest was useful in the management of hypoxaemia in patients with atelectasis or pneumonia and that improved ventilation / perfusion (V/Q) balance was the reason for the observed significant increase in PaO_2 30 and 60 minutes after treatment (Holody and Goldberg, 1981). Yet another study showed a decrease in intrapulmonary shunt and significant improvement in respiratory compliance 2 hours after physiotherapy in 19 mechanically ventilated patients with post-traumatic respiratory failure (Mackenzie and Shin, 1985).

1.2.2.7 Potentially adverse effects of multimodality treatments

The physiological and haemodynamic effects of physiotherapy have been extensively investigated. Some of these will be described later under the heading of specific

treatment modalities. Several authors have reported arrhythmia's during or following suction or physiotherapy (Hammon et al. 1992), while others have found that patients without adequate sedation have had significant and sometimes dramatic increases in heart rate, blood pressure, cardiac output, oxygen consumption (VO_2), carbon dioxide elimination (VCO_2) and $PaCO_2$ during such treatments. Some of these studies described significant reduction in certain or all of these effects with sedation or pharmacological paralysis (Bodai, 1982; Weissman et al. 1984; Klein et al. 1988; Stone et al. 1991; Hammon et al. 1992; Weissman and Kemper, 1993; Harding et al. 1994; Weissman et al. 1994; Singer et al. 1994; Cohen et al. 1996; Horiuchi et al. 1997).

Physiotherapy and suction treatments have also been associated with significant increases in intracranial pressure (ICP), although in most cases, the simultaneous increase in blood pressure has resulted in adequate or only transiently inadequate cerebral perfusion pressures (CPP) (Parsons and Shogan, 1984; Garradd and Bullock, 1985; Durand et al. 1989; Singh et al. 1991; Crosby and Parsons, 1992; Paratz and Burns, 1993; Wang et al. 1993; Brucia, 1993; Brucia and Rudy, 1996; Imle et al. 1998). Adequate sedation and pharmacological paralysis have been reported effective at controlling these responses to tracheal suction (Parsons and Shogan, 1984; Ninan et al. 1986; Ninan et al. 1986; Fanconi and Duc, 1987; Ersson et al. 1990). Brimioulle et al claimed that passive mobilisation techniques were not associated with adverse effects in patients with raised ICP (Brimioulle et al. 1997).

In 1998, Harding et al proposed a connection between encephaloclastic porencephaly and chest physiotherapy in extremely preterm infants (Harding et al. 1998). The study involved retrospective analysis of 454 infants of birth weight less than 1500gm delivered between 24 to 27 weeks of gestation. Patients with encephaloclastic porencephaly received two to three times as many chest physiotherapy treatments in the second, third, and fourth weeks of life as control infants ($p < 0.001$). Affected subjects also had more prolonged and severe hypotension in the first week than control subjects ($p < 0.01$), and were less likely to have had a cephalic presentation ($p < 0.01$). The brain lesion was considered by the authors to be caused by impact of the brain with the skull during shaking movements that could occur during chest physiotherapy with percussion. Since the publication by Harding, several authors have disputed the connection between

encephaloclastic porencephaly and physiotherapy and have also pointed out the significant methodological errors and risks of type 1 error in this work (Beeby et al. 1998; Gray et al. 1999; Vincon, 1999). Gray et al and Beeby et al reported that they had not found any cases of encephaloclastic porencephaly over the same 3-year period, despite similar criteria for the initiation of physiotherapy treatment. Gray noted that while Harding found a strong association ($P < 0.001$) between chest physiotherapy and encephaloclastic porencephaly, severe hypotension and noncephalic presentation were also statistically significant and the "model collapsed" when these variables were entered into the multivariate analysis. It was thus likely that the lesion occurred only in the sickest infants and the fact that they had more chest physiotherapy just reflected their degree of illness.

1.2.3 The efficacy of individual components of physiotherapy treatments in ventilated patients.

Most frequently physiotherapy treatments involve a combination of treatment techniques. Research attempting to tease out the effects of different components of treatment rarely tests each component in isolation. Instead they involve designs where a specific technique is included or not in a control group and then the differences between the groups are attributed to the specific technique. There are several treatment modalities commonly used in ventilated children which include those discussed below.

1.2.3.1 Positioning and postural drainage

Postural drainage refers to therapeutic drainage in bronchopulmonary diseases in which there is copious mucus secretion, such as chronic bronchitis, bronchiectasis, pulmonary abscess, or cystic fibrosis. The patient is placed so that gravity assisted drainage of the affected lobe may be facilitated. There are eleven described therapeutic positions which have the aim of allowing gravity to assist in accelerating drainage of mucus from the lung periphery to larger airways. The duration of postural drainage may vary considerably (15 - 60 minutes) depending on the age and tolerance of the patient as well as the clinical requirements of the treatment (Bateman et al. 1981; Ciesla, 1996). Results from some studies on non-ventilated adults claim that postural drainage adds benefit to traditional chest physiotherapy (Sutton et al. 1982; Johnson et al. 1987). One study found that postural drainage and manual hyperinflation in ventilated patients did not reduce the risk of nosocomial pneumonia (Ntoumenopoulos et al. 1998), but no other

studies reporting the efficacy of these techniques in adult or paediatric intensive care have been found.

Chest physiotherapy including postural drainage has been implicated in causing or exacerbating gastro-oesophageal reflux in young patients with cystic fibrosis (Button et al. 1997; Taylor and Threlfall, 1997; Heine et al. 1998; Button et al. 1998; Button, 1999), but this effect has been disputed by others (Phillips et al. 1998) and was not found in patients with chronic bronchitis and bronchiectasis (Chen et al. 1998).

Positioning refers to the more general aim of optimising V/Q matching, and the physiological rationale for it in the intensive care unit has been well described in some disorders. Prone positioning has been shown to improve oxygenation in the short term in critically ill adults and children (Langer et al. 1988; Pappert et al. 1994; Mizuno et al. 1995; Chatte et al. 1997; Mure et al. 1997; Numa et al. 1997; Jolliet et al. 1998; Mizuno and Aizawa, 1999). Improvements in lung function have also been described for patients with unilateral lung disease when they are positioned in side lying, although the optimal position is different in adult and paediatric patients because of differences in regional ventilation and perfusion (Zack et al. 1974; Ibanez et al. 1981; Prokocimer et al. 1983; Rivara et al. 1984; Gillespie and Rehder, 1987; Larsson et al. 1989; Lumb and Nunn, 1991; Webster, 1999). In children and adults, the effect of posture on the distribution of perfusion is similar, however, in children ventilation in response to gravity is the reverse of that seen in adults, being preferentially distributed to the upper lung whether diseased or normal (Heaf et al. 1983; Davies et al. 1985; Bhuyan et al. 1989). Positioning therapy to assist resolution of acute atelectasis has been recommended, but the evidence for this is unclear (Dean, 1985; Dean and Ross, 1992; Dean, 1997).

1.2.3.2 Manual hyperinflation, hyperventilation or hyperoxygenation

Manual lung inflation involves disconnection of the patient from mechanical ventilation to provide temporary manual ventilation. Specific techniques of performing manual inflation depend on whether the aim is to achieve hyperinflation, hyperoxygenation, hyperventilation or a combination of these.

Manual hyperinflation commonly involves a slow, deep inspiration, inspiratory pause and fast unobstructed expiration, although the technique should be modified for patients with reduced or compromised cardiac output. Specific aims of this procedure are to improve tidal volume and alveolar recruitment by re-inflating areas of atelectasis, thereby improving compliance and ventilation/perfusion matching. Hyperinflation will additionally often stimulate cough in self ventilating patients and thus assist in airway clearance (Clement and Hubsch, 1968; Windsor et al. 1972; Bartlett et al. 1973; Stiller et al. 1996). Hyperinflation manoeuvres have been shown to effectively re-expand collapsed lung tissue and improve oxygenation in anaesthetised ventilated adults with healthy lungs (Rothen et al. 1999).

Research examining the efficacy of manual hyperinflation specifically in airway clearance is conflicting or not comparable because of significant differences in technique and methodology (Barker and Eales, 2000). Controversy exists regarding the safety and effectiveness of application of manual lung hyperinflation in intubated patients. Tidal volumes, pressures and FiO_2 are not controlled and there are inherent dangers of barotrauma or hypoxaemia in the absence of additional oxygen (Brandstater and Muallem, 1969; Fox et al. 1978; Gattinoni et al. 1993; McKelvie, 1998; Clarke et al. 1999; Dorges et al. 2000). Whereas some studies suggest that the addition of manual hyperinflation in treatment does not offer any advantage (Novak et al. 1987; Eales et al. 1995), others have found that manual hyperinflation was associated with an improvement in respiratory compliance and sputum clearance in mechanically ventilated patients without compromise of cardiovascular stability or gas exchange (Jones et al. 1992; Hodgson et al. 2000).

Hyperoxygenation involves delivering greater FiO_2, with the purpose of improving oxygenation. It may be used in combination with manual hyperinflation during physiotherapy treatments and is recommended in preference to hyperinflation alone in reducing suction-induced hypoxaemia, or facilitating recovery after suction (Chulay and Graeber, 1988; Lookinland and Appel, 1991). Stone and others, comparing the efficacy of ventilator versus manual hyperinflation in delivering hyperoxygenation or hyperinflation breaths before, during, and/or after tracheal suctioning, found that ventilator delivered breaths were either superior or equivalent to manually delivered

breaths in preventing suction-induced hypoxaemia, and that delivery of manual hyperinflation breaths resulted in increased airway pressure and increased haemodynamic consequences (Stone, 1990; Grap et al. 1996). By contrast, Goodnough (1985) claimed that manual hyperinflation with FiO_2 of 1 provided better protection than ventilator delivered breaths of the same FiO_2, but recommended monitoring of haemodynamic parameters because of potential alterations in arterial blood pressure and heart rate associated with manual hyperinflation (Goodnough, 1985).

Manual hyperventilation involves rapid delivery of breaths usually with the aim of improving oxygenation or blowing off CO_2. It is rarely used in physiotherapy treatments, but may be helpful in patients in whom hypercapnia should be avoided, for example patients with head injuries in whom low $PaCO_2$ may be advantageous prior to treatment, or patients in pulmonary hypertensive crisis who have extremely reduced C_{rs} and may be difficult to oxygenate. The efficacy of hyperventilation in physiotherapy treatments has not been reported.

1.2.3.3 Chest percussion (clapping) and vibrations

Chest percussion or clapping in paediatric patients involves tapping the chest wall with cupped hand, fingers or soft plastic cuff to mobilise secretions. Vibrations refer to the manual technique of shaking the chest wall during the expiratory phase of respiration. Chest percussion or vibrations are reported to enhance mucociliary clearance from central and peripheral airways (May and Munt, 1979; Bateman et al. 1981; Mackenzie et al. 1989; Ambrosino et al. 1995). The exact mechanisms by which percussion and vibration are felt to achieve mucociliary clearance are unclear, but alteration of airflow and release of pulmonary chemical mediators have been proposed (King et al. 1983; Gallon, 1991). At bronchoscopy, secretions have been seen to move into the upper airways when vibrations are applied to the chest wall (Ciesla, 1996). Other authors have suggested that chest wall vibrations and manual hyperinflation are associated with large fluctuations in cardiothoracic pressure and hence are inadvisable (Laws and McIntyre, 1969).

Some studies assessing the efficacy of percussion and vibrations in ventilated adults and infants have found a significant increase in PaO_2 while pH or $PaCO_2$ were unaffected

(Finer and Boyd, 1978; Holody and Goldberg, 1981). Another study, however, found a significant fall in PaO_2 after chest percussion in ten patients who produced no sputum or small amounts of sputum, while there was no significant change in PaO_2 in 12 patients who produced moderate to large amounts of mucopurulent secretions (Connors et al. 1980). Some authors suggested that in non-ventilated patients postural drainage was the most useful therapeutic component while percussion and vibrations had nothing to add (Kirilloff et al. 1985; Sutton et al. 1985; Pavia, 1990).

Bronchospasm, increased risk of arrhythmia, decreased blood pressure, increased heart rate and short term decline in FEV_1 (forced expiratory volume) have all been associated with percussion in both ventilated and non-ventilated patients (Campbell et al. 1975; Wollmer et al. (b) 1985; Hammon et al. 1992; Ntoumenopoulos, 1994). Pharmacological bronchodilation therapy has been proposed in cases where the benefits of treatment are thought to outweigh the risks of bronchospasm (Gallon, 1991).

1.2.3.4 Instillation of saline

Saline instillation into the tracheal tube of ventilated patients is commonly used to stimulate cough or loosen thick, sticky secretions so that they may easily be removed with suction, but evidence for the practice is equivocal (Swartz et al. 1996; Schwenker et al. 1998). Some authors suggest that at best saline instillation is not effective and at worst may be detrimental in terms of O_2 saturation (Bostick and Wendelgass, 1987; Ackerman, 1993; Hagler and Traver, 1994; McKelvie, 1998; Ackerman and Mick, 1998; Blackwood, 1999; Kinloch, 1999), while others suggest it is well tolerated even in infants and may be helpful in removing secretions adherent to the chest wall (Shorten et al. 1991; Whitnack, 2000). Several reviews suggest normal saline instillation in ventilated patients should be discontinued as a routine or standard practice until more research has proved its efficacy (Raymond, 1995; Druding, 1997).

1.2.3.5 Tracheal suction

Tracheal suctioning is a necessary practice carried out in intensive care units. It involves the removal of pulmonary secretions from a patient with an artificial airway in place via a catheter connected to a negative pressure source (Stone and Turner, 1989). Sometimes suction is used to stimulate a cough in patients making spontaneous ventilatory efforts who have a poor cough reflex. It has been shown that despite its

usefulness in the management of ventilated patients, suction can be associated with many detrimental effects including hypoxaemia, mechanical trauma, apnoea, bronchospasm, pneumothorax, atelectasis, cardiac arrhythmia, fluctuations in ICP, infection and even death on rare occasions (Brandstater and Muallem, 1969; Fox et al. 1978; Young, (a) 1984; Stone and Turner, 1989; Shorten, 1989; Clark et al. 1990; Jaw et al. 1991; Czarnik et al. 1991; Mehrabani et al. 1991; Paratz, 1992; Singer et al. 1994; Boothroyd et al. 1996; Clarke et al. 1999). Accepted methods for reducing complications associated with suction include pre-oxygenation, adequate sedation, reassurance and suctioning via a port adapter or closed suction system in patients who require maintenance of PEEP and/or positive pressure ventilation during suction (Urban and Weitzner, 1969; Cabal et al. 1979; Bodai, 1982; Brown et al. 1983; Goodnough, 1985; Graff et al. 1987; Chulay and Graeber, 1988; Harshbarger et al. 1992; Mancinelli-Van and Beck, 1992). Pre-oxygenation with ventilator breaths has been recommended above disconnection and manual hyperinflation because of the reduced risk of barotrauma, loss of PEEP and FiO_2 (Chulay and Graeber, 1988; Stone et al. 1991; McCabe and Smeltzer, 1993; Glass et al. 1993).

1.2.4 Evidence for physiotherapy treatments being better than nursing suction alone.

There are few publications which examine the differences between respiratory physiotherapy and nursing suction, or whether physiotherapy should be provided routinely or selectively in addition to routine nursing care. Interpretation of these studies is made more difficult by the variability in techniques between units and the overlap between nursing and physiotherapy practice in many cases.

One study of patients with acute lobar atelectasis compared hyperinflation and suction alone with treatments that comprised positioning, vibrations, hyperinflation and suction. Fourteen cases were alternately allocated to either physiotherapy regimen, which were performed hourly for 6 hours. After one treatment, patients in the intensive treatment group showed a mean 60% resolution of their atelectasis as seen on chest radiographs, compared with a 7.6% resolution in the non active group. After the six-hour treatment period, the difference between the groups remained significant although less so, but after 24 and 48 hours, the difference between groups was not significant. These results

suggest that, at least initially in the course of acute lobar atelectasis, positioning and vibrations add to the efficacy of a treatment of hyperinflation and suction alone (Stiller et al. 1990).

Another study randomised 46 patients to receive physiotherapy and nursing suction, or nursing suction alone. Twice as many patients developed nosocomial pneumonia in the nursing only group (8/24) compared with the physiotherapy group (4/22) although the differences were not statistically significant, ($p = 0.24$). The length of ventilation time and ICU stay were similar and there were no differences in pulmonary dysfunction between the two groups (Ntoumenopoulos et al. 1998). Although physiotherapy was not associated with a reduced incidence of nosocomial pneumonia in this study, the trend to more frequent nosocomial pneumonia in the control patients suggests that a larger study might have revealed different results.

A review of physiotherapy practice in Australia found that although the methods of chest treatment and the indicators for commencing chest treatment were similar in neonatal intensive care units, clinical techniques and protocols for chest physiotherapy varied greatly between units. The results revealed that both physiotherapists and nursing staff played a role in the performance of chest treatment in all but one unit where it was the responsibility of nursing staff. However, the greatest variability between neonatal intensive care units was in the individual treatment protocols employed pre- and post-extubation of the neonate. It was concluded that further well-controlled studies with larger sample sizes were needed to validate the use of chest physiotherapy for the neonate, especially in relation to the techniques and specific protocols employed (Lewis et al. 1992). This study highlighted the considerable inconsistency and overlap between physiotherapy and nursing suction practices and the need for careful definition of terms of practice both in research and clinical management.

A questionnaire survey distributed to nurses and physiotherapists at the Royal Hospital for Sick Children in Edinburgh revealed that there was significant disagreement over paediatric nasopharyngeal suction in terms of appropriate catheter size, suction pressure and method of suction as well as use of pre-oxygenation and knowledge of adverse effects. The paper concluded that further theoretical and practical education was needed

in the use of nasopharyngeal suction and that a standard method should be implemented throughout the hospital (Macmillan, 1995). This study was specific to one institution, but highlighted an issue likely to be equally relevant to others both nationally and internationally.

1.2.5 Evidence to support the use of respiratory function testing in the paediatric intensive care unit.

While there is little evidence to date to suggest that routine measurements of respiratory function reduce either morbidity or mortality on the ICU, they could make an important contribution to the management of ventilated infants by improving understanding of pulmonary physiology, and the response of the paediatric lung to different types of ventilatory support and therapeutic interventions, including physiotherapy and nursing suction. Respiratory function monitoring has a potential role in monitoring the course of the disease, assessing the effects of treatments and guiding appropriate ventilation settings. In addition there may be potential for using respiratory monitoring for diagnostic purposes (classification, prognosis, choice of treatment) (Sly et al. 1996). The technological advancement of ventilators for children has been impressive in the last decade. Developing in parallel have been the "stand alone" and integrated respiratory monitors which facilitate continuous analysis and display of a variety of respiratory parameters. The range of respiratory function tests that can be performed on the ventilated patient is considerable and several investigations which previously required complex equipment have now been incorporated into modern ventilators and respiratory monitors. The accuracy and validity of many of these systems has yet to be established, but this is an essential prerequisite before attempts can be made to assess their clinical efficacy and usefulness (Gerhardt and Bancalari, 1991; Petros et al. 1993; Greenough, 1994; Numa and Newth, 1995; Hammer and Newth, 1995; Macnaughton, 1997). There are many factors which have the potential to confound measurements of respiratory function in ventilated patients including tracheal tube leak, site of measurements, posture and spontaneous ventilatory effort. These all need to be considered during measurements and interpretation of data obtained from mechanically ventilated children (Kuo et al. 1996; Kondo et al. 1997).

The American Thoracic Society has established technical standards and testing procedures for equipment used in older subjects (American Thoracic Society, 1995; American Thoracic Society, 1986), but until recently, there have been no such standards for neonatal monitoring equipment. This could result in inaccurate calibration and software problems as well as unsuitable equipment characteristics with respect to deadspace, resistance and frequency response (Jackson et al. (b) 1995). Last year two papers defined minimal performance criteria for signal processing and data handling used to measure respiratory function in infants. Guidelines such as these should ensure that infant lung function measurements can be performed with an acceptable degree of safety, precision, and reproducibility. They have the potential to facilitate multicentre collection of data and improve the quality of clinical investigations (Frey et al. (a) 2000; Frey et al. (b) 2000).

Despite the lack of technical standards and thorough validation, the perceived benefits of respiratory function testing in ventilated infants over recent years have included the ability to modify ventilation settings to optimise ventilator/patient interaction, evaluation of disease severity, prognosis and the efficacy of many therapies including surfactant (Edberg et al. 1990; Goldman et al. 1992; Pfenninger et al. 1992; Armsby et al. 1992; Freezer and Sly, 1993; Kelly et al. 1993; Tarnow-Mordi et al. 1994; Greenough, 1994; Amato et al. 1998; Migliori et al. 1999).

1.2.5.1 Tidal breathing parameters

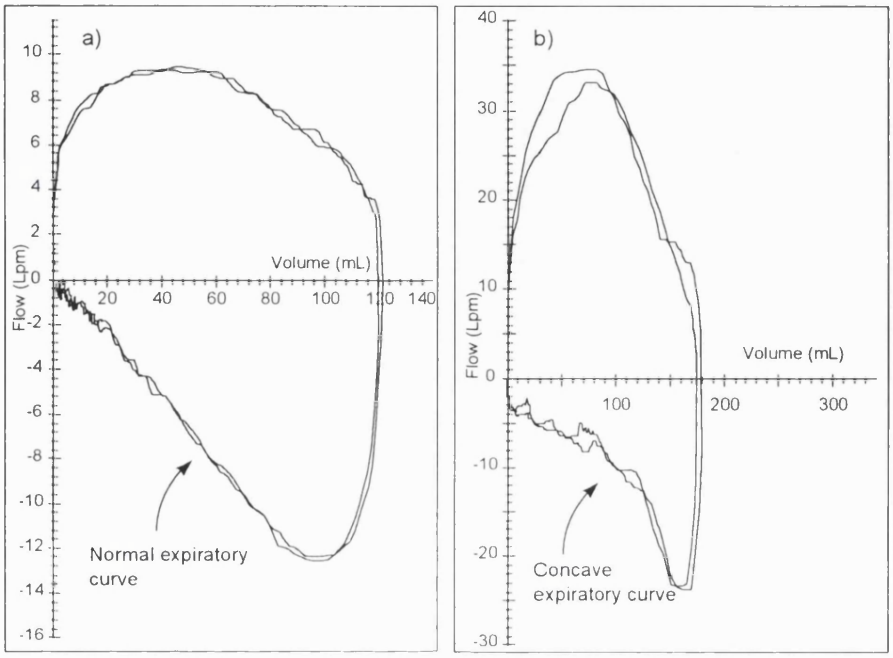
Measurement of tidal breathing parameters may be useful in assessing lung physiology or the effect of ventilator settings (Hammer and Newth, 1995). Measurements of flow and volume are relatively simple to perform but numerous factors may influence the accuracy of these recordings including the method and site of measurement, gas compression in the ventilator circuit, the activity of the patient and tracheal tube leak which may be unpredictable and difficult to measure or detect (Hjalmarson, 1994). Conventional intratracheal flowmeters do not give linear output signals for the actual flow. This may be solved by the use of a larger flowmeter close to the tube connector although this will increase deadspace, or by a software programme which allows automatic linearisation with small flowmeters. Flowmeters are sensitive to changes in

gas composition and may be inaccurate when used within a pressurised system (Le Souëf et al. 1984).

Modern ventilator designs often incorporate a flowmeter into the ventilation circuit which provides continuous feedback about tidal breathing or respiratory mechanics. Several authors have reported that V_{TE} measured with a conventional ventilator at the expiratory valve was systematically overestimated and correlated poorly with V_{TE} measured with a flowmeter placed at the tracheal tube. The ventilator value was a poor indicator of delivered V_T and in conventionally ventilated infants, V_{TE} should be determined with a flowmeter placed at the airway. In addition, the compliance of the ventilator circuit is a significant factor in determining delivered V_T. Given the small tidal volumes used, small errors in V_T could have significant adverse consequences for small infants (Kreit and Sciurba, 1996; Stevenson et al. 1998; Cannon et al. 2000; Stayer et al. 2000; Chow et al. 2000). Peak inspiratory pressures reported by infant ventilator manometers have also been found to consistently underestimate true peak pressures delivered to the proximal airway (Sola et al. 1992).

A number of ventilators display inspiratory and expiratory flow volume curves. The shape of these curves may alert the clinician to a number of abnormalities including significant airway secretions, auto PEEP, ventilation inhomogeneity and expiratory flow limitation. A concave shape towards the baseline of the expiratory curve is a sensitive indicator of expiratory flow limitation (Figure 1-1) and therefore of intrinsic PEEP, whereas a sawtooth pattern appears to be associated with the presence of airway secretions (Brown et al. 1989; Jubran and Tobin, 1994; Valta et al. 1994).

Figure 1-1: Flow volume curves in a) a patient with normal lungs and b) a child with asthma and expiratory flow limitation.



Intrinsic PEEP may be detected in patients with obstructive airways disease or ARDS undergoing mechanical ventilation, and the clinical consequences of intrinsic PEEP include increased inspiratory work of spontaneous breathing, reduced ability to trigger the ventilator, the haemodynamic effects of increased intra-thoracic pressure and an increased risk of barotrauma (Rossi et al. 1995).

1.2.5.2 Respiratory mechanics

While measurements of dynamic mechanics became established in the 1950's, it was only with significant advances in computer technology during the 1980's that complex methods of analysis became possible using least-squares regression (Uhl and Lewis, 1974; Mortola et al. 1982; Mortola and Saetta, 1987) and multiple linear regression (Bhutani et al. 1988). With new computer technology, continuous measurements of pulmonary mechanics are now readily available and have been found to be reproducible in mechanically ventilated adults and children (Ratjen and Wiesemann, 1992; Rosen et al. 1993; Numa and Newth, 1995; Gonzalez et al. 1996; Polese et al. 1999).

One of the goals of measuring respiratory mechanics and lung volumes in the ICU is to assess the response to clinical therapies and interventions, thereby allowing rapid

responses to ensure optimal management of the patient and the ability to predict the likelihood of successful weaning (Garg et al. 1991; Hjalmarson, 1994; Kugelman et al. 1995; Hammer and Newth, 1995; Macnaughton, 1997).

A recent review of the clinical relevance of monitoring respiratory mechanics in the ventilated patient concluded that assessment of respiratory mechanics had assisted in the understanding of patient-ventilator relationships and pathophysiology and would be very useful in terms of adopting new ventilation strategies (Appendini and Marco, 2001).

1.2.5.2.1 Respiratory Compliance

A retrospective study about the theoretical benefits of matching ventilatory support to the requirements indicated by respiratory mechanics (whereby the most efficient ventilation could be administered while minimising lung overdistension), found that those infants managed by monitoring pulmonary mechanics had fewer pneumothoraces and grade I-II intraventricular haemorrhages (IVH) than infants who were managed prior to this "measurement-response regimen". However the incidence of pulmonary interstitial emphysema (PIE) and bronchopulmonary dysplasia (BPD) was similar, as were survival rates, length of time on mechanical ventilation and length of stay in hospital (Rosen et al. 1993).

A prospective randomised controlled trial was conducted to determine if outcomes could be improved in neonates requiring mechanical ventilation if regular pulmonary function tests were performed. One group received conventional clinical management while the other received conventional management and regular measurements of C_{rs}. No significant differences in terms of the duration that oxygen and mechanical ventilation were needed, the frequency of the development of chronic lung disease, the pattern of cranial ultrasound abnormality or the length of hospital stay were found between the two groups. The study concluded that measurements of pulmonary mechanics may be of limited use, but conceded that some of the staff were not used to interpreting the information provided in a relatively new way and that the frequency of C_{rs} measurements (once a day) was insufficient for producing differences in clinical outcomes (Stenson et al. 1998).

The values of total C_{rs} in ventilated adults and children with acute respiratory failure may be considerably reduced due to reductions in both chest wall and lung compliance and may be used to predict outcome (Hjalmarson, 1994; Pelosi et al. 1995). Some studies claim C_{rs} measurements have been useful in selecting neonates for surfactant therapy, assessing the response to surfactant, the assessment and management of patients with ARDS as well as guiding appropriate ventilator management and setting optimal levels of tidal volume and PEEP (Wilkie et al. 1994; Numa and Newth, 1995; Smith et al. 1999; Jonson et al. 1999; Lemaire, 2000; Nikischin et al. 2000). However, others claim C_{rs} measurements have not been shown to predict success of extubation or surfactant therapy (Hjalmarson, 1994).

1.2.5.2.2 Respiratory Resistance

Significant increases in respiratory resistance (R_{rs}) have been described in patients with ARDS, cardiac failure, chronic airflow limitation, bronchospasm, airway wall oedema and those in whom air flow has been acutely compromised because of secretions within the airway lumen, intra-lumenal obstruction or extra-lumenal compression. Assessment of R_{rs} has been clinically useful in interpreting the cause of increased airway pressure during mechanical ventilation, in assessing responses to bronchodilator or other therapies and predicting successful extubation (Broseghini et al. 1988; DiCarlo et al. 1992; Pelosi et al. 1995; Dhand and Tobin, 1997). Resistance of the respiratory system varies more within and between individuals than does compliance, and these differences may be explained by non laminar flow and the length and degree of compression of the tracheal tube or fluctuations in airway smooth muscle tone (Hjalmarson, 1994).

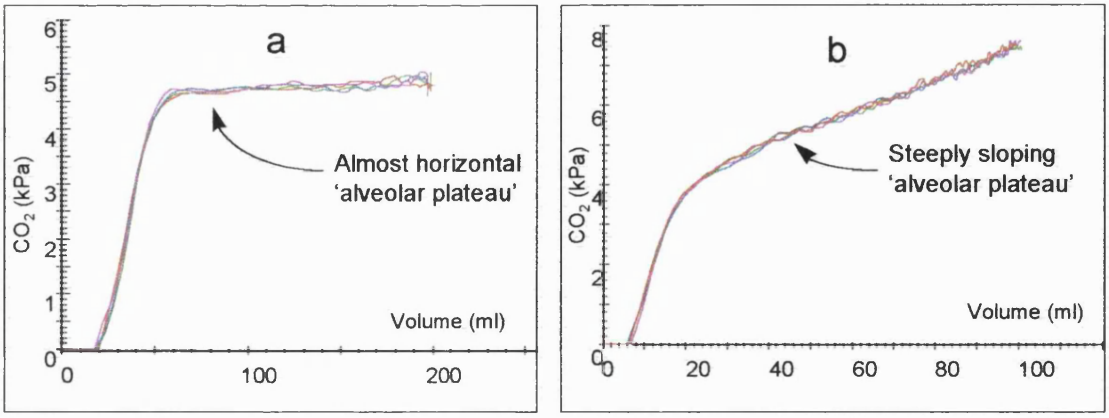
1.2.5.3 CO_2 Monitoring

The role of $ETCO_2$ monitoring as an alternative to measuring $PaCO_2$, has been investigated at length because $ETCO_2$ monitoring is easily available and is non-invasive. While some studies suggest that $ETCO_2$ and $PaCO_2$ may sometimes be used interchangeably (Tobias et al. 1994; Campbell et al. 1994; Flanagan et al. 1995; Imai et al. 1996; Nangia et al. 1997; Ozlu and Ocal, 1999; Bhavani-Shankar et al. 2000), others have noted that there are many clinical scenarios in which $ETCO_2$ is inaccurate at predicting $PaCO_2$, especially in critically ill patients or those with significant pulmonary or cardiac disease (Lindahl et al. 1987; Burrows, 1989; Fletcher, R.1991; Jellinek et al.

1993; Russell and Graybeal, 1994; Kerr et al. 1996; Pianosi and Hochman, 1996; Prause et al. 1997; Laffon et al. 1998). The reasons for a mismatch between $ETCO_2$ and $PaCO_2$ in a changing clinical scenario reflect changes in V/Q matching and physiological deadspace (Yamanaka and Sue, 1987; Taskar et al. 1995). A prerequisite for proportionality between $ETCO_2$ and $PaCO_2$ is a constant V/Q relationship which would leave deadspace unchanged. Other reasons may include failure of $ETCO_2$ to equilibrate with alveolar gas as a result of airway obstruction, rapid respiratory rate or short expiratory time. Despite these problems, a rising or falling $ETCO_2$ remains potentially useful as a continuous and non-invasive indicator of change in respiratory function during mechanical ventilation.

Several authors have suggested the shape of the single breath CO_2 curve ($SBCO_2$) might yield valuable information about gas exchange, airway pathology and ventilation inhomogeneity (Figure 1-2) in patients with respiratory disease, and that because the method is simple and non-invasive, it has promising applications in young children and infants (Fletcher et al. 1981; Schreiner et al. 1993; You et al. 1994; Ream et al. 1995; Kars et al. 1997; Olsson et al. 1999; Stromberg and Gustafsson, 2000).

Figure 1-2: Comparison between $SBCO_2$ curve in a) a patient with normal lungs and b) a child with severe asthma



The almost simultaneous emptying of CO_2 from alveoli in normal lungs is reflected in the horizontal phase III of the $SBCO_2$ plot (a), whereas the ventilation inhomogeneity and delayed emptying of CO_2 from alveoli in patients with asthma is reflected in the steeply sloping phase III in plot (b).

In addition, the $SBCO_2$ curve allows an estimation of $V_{D_{phys}}$ and $V_{D_{airway}}$. Several adult studies have suggested that the shape of the $SBCO_2$ curve and calculation of $V_{D_{alv}}$

would be useful in the diagnosis of acute pulmonary embolism, based on the fact that the large amount of wasted ventilation would be reflected in the large $V_{D_{phys}}$ or raised V/Q ratio (Eriksson et al. 1985; Wollmer et al. (a) 1985; Fletcher R, et al. 1986; Fletcher and Jogi, 1986; Burki, 1986; Eriksson et al. 1989; Olsson et al. 1998; Kline and Arunachlam, 1998; Johanning et al. 1999; Kline et al. 2001).

1.2.5.4 Deadspace measurements

Pulmonary deadspace (defined in section 2.4) refers to the ventilated areas of the lung or upper respiratory tract which do not participate in gas exchange (wasted ventilation). This includes mechanical deadspace which is composed of external artificial airways. The relationship between ineffective versus effective volume (V_D/V_T) can be calculated for different deadspace components or for total deadspace. Deadspace volumes correlate positively with body weight, height and body surface area (Shenkman et al. 1996; Puri et al. 1999) and are affected by body and neck position, alveolar volume at end of expiration, V_T, intubation status, ventilation modality and length of tracheal tube (Marsh et al. 1973; Klingstedt et al. (a) 1990; Klingstedt et al. (b) 1990; Casati et al. 1997; Neto et al. 2000).

Methods for calculation of respiratory deadspace include collection of CO_2 expired in a Douglas bag or use of the modified Bohr equation (Equation 2-6). The accuracy of deadspace measurements using a metabolic monitor has been shown to compare favourably to the traditional Douglas bag method thus providing a convenient and simple alternative (Fletcher and Jonson, 1984; Kiiski et al. 1991; Arnold et al. 1993; Arnold et al. 1996; Lum et al. 1998).

Bronchoalveolar lavage in rabbits has been found to elevate $V_{D_{alv}}$, $V_{D_{phys}}$ and the deadspace/tidal volume ratios and is associated with a fall in the arterial/alveolar PO_2 ratio. Surfactant treatment improves gas exchange but does not restore the lung to its pre-bronchoalveolar lavage condition, which indicates that the exogenous surfactant only partially affects the recruitment of the atelectatic areas (Wenzel et al. (a) 1999). Children with cyanotic congenital heart disease had significantly larger $V_{D_{phys}}/V_T$ than normal children or those with acyanotic heart disease ($p< 0.01$) (Mecikalski et al. 1984;

Fletcher and Jogi, 1986; Lindahl et al. 1987; Bermudez and Lichtiger, 1987; Burrows, 1989; Fletcher, 1989; Arnold et al. 1996)

Measurements of respiratory deadspace have been useful in predicting successful weaning from mechanical ventilation in some adult and paediatric patients (Hardman and Aitkenhead, 1999; Hubble et al. 2000) and may also have the potential to provide important prognostic information in infants with congenital diaphragmatic hernias (Arnold et al. 1995) or to provide non-invasive estimates of cardiac output (Arnold et al. 1996). Quantification of alveolar deadspace may be directly related to the effectiveness of pulmonary perfusion (Severinghaus et al. 1998).

1.2.5.5 Blood gases

Blood gas analysis allows for the qualitative and quantitative assessment of the efficacy of gas exchange and both metabolic and respiratory acid-base problems, including the interrelationships between ventilation, oxygenation, and metabolic conditions. Blood gas analysis is a useful adjunct to clinical patient assessment and other diagnostics in determining appropriate therapy for specific and complex conditions.

Arterial blood gases have remained the mainstay of respiratory function monitoring in the intensive care unit, however because of their invasive nature, other systems are constantly being investigated as efficient alternatives (Harrison et al. 1997). Clinical scoring systems of respiratory distress are not easy to establish because the clinical signs are few and non specific. Cyanosis is not easily recognised until saturations fall close to 70%, corresponding to a PaO_2 of about 5.32kPa. Hypercapnea has no clinical signs until it is dangerously far advanced. Arterial blood gases are the prime determinants of the need to intubate, change ventilation or extubate (Numa and Newth, 1995).

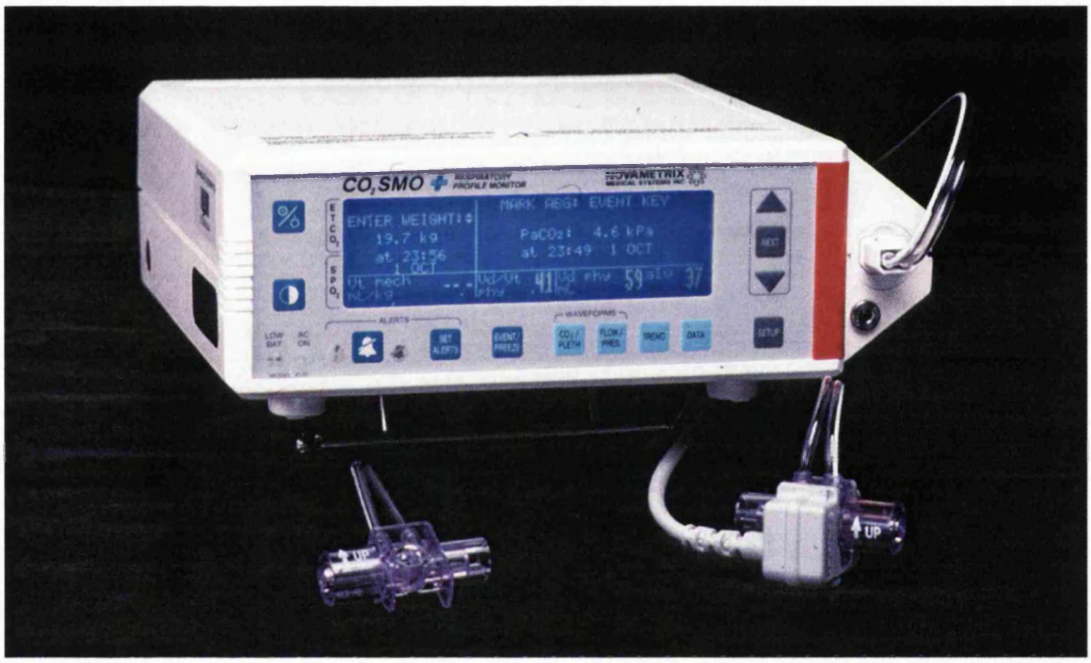
The lack of continuous monitoring still makes it difficult to assess acute changes in hypoxia and hypercapnea. However, the development of portable bedside blood gas analysers (Sediame et al. 1999) and more recently, the continuous intra-arterial fibre-optic blood gas monitoring systems have allowed almost immediate or immediate assessment of respiratory status (Numa and Newth, 1995).

In summary, there remain large gaps in our knowledge about the effects of physiotherapy on respiratory function in ventilated children. The recent availability of potential tools for measurement of respiratory function have made it possible to attempt to answer some of the questions regarding the use and effects of physiotherapy treatments. Combinations of the therapies described above were included for assessment in this study and tidal volumes, C_{rs}, R_{rs}, deadspace volumes, CO_2 parameters and arterial blood gases were selected as outcome measures in appraising the efficacy of physiotherapy and nursing suction procedures. The following chapter examines the theoretical background, methods of measurement and algorithms employed in calculation of these parameters by the "CO_2SMO Plus".

2. Outcome measures: theoretical background

At the inception of this thesis, the "CO_2SMO Plus" respiratory monitor (Figure 2-1) was a relatively new portable device for measurements of respiratory function. Potential advantages of this device as a research tool included the capacity to measure and store recorded data electronically so that subsequent analysis could be performed. In addition, measurements were non-invasive and made at the mouth of the tracheal tube, and thus avoided the potential measurement errors associated with gas compression in the ventilator tubing (Cannon et al. 1999).

Figure 2-1: The "CO_2SMO Plus" respiratory monitor with flow sensor and infra-red capnography device.



The neonatal flow sensor shown in right foreground with the infra-red CO_2 sensor straddling the combined flow-pressure transducer and in the left foreground without the CO_2 sensor

The "CO_2SMO Plus" directly recorded four variables: flow, pressure, time and CO_2 concentration. Flow and pressure were measured instantaneously through an integrated fixed orifice differential flow-pressure transducer, thereby minimising potential problems related to time lag. Data were electronically recorded by a 20 bit resolution, 100 Hz flow data sampling microprocessor. The time signal was generated from the "CO_2SMO Plus" internal clock. The CO_2 concentration was measured in real time by a

mainstream solid state CO_2 sensor which used a beam splitter to simultaneously measure infra red light at two wavelengths: one which was absorbed by CO_2 and one which was not. The simultaneous measurement of these variables allowed generation of wave-forms and integrated respiratory parameters such as tidal volume (V_T), respiratory resistance (R_{rs}), respiratory compliance (C_{rs}) and deadspace measurements. All parameters were calculated in body temperature and pressure saturated (BTPS) units.

2.1 Ventilatory parameters: Flow, respiratory rate, pressures and volumes.

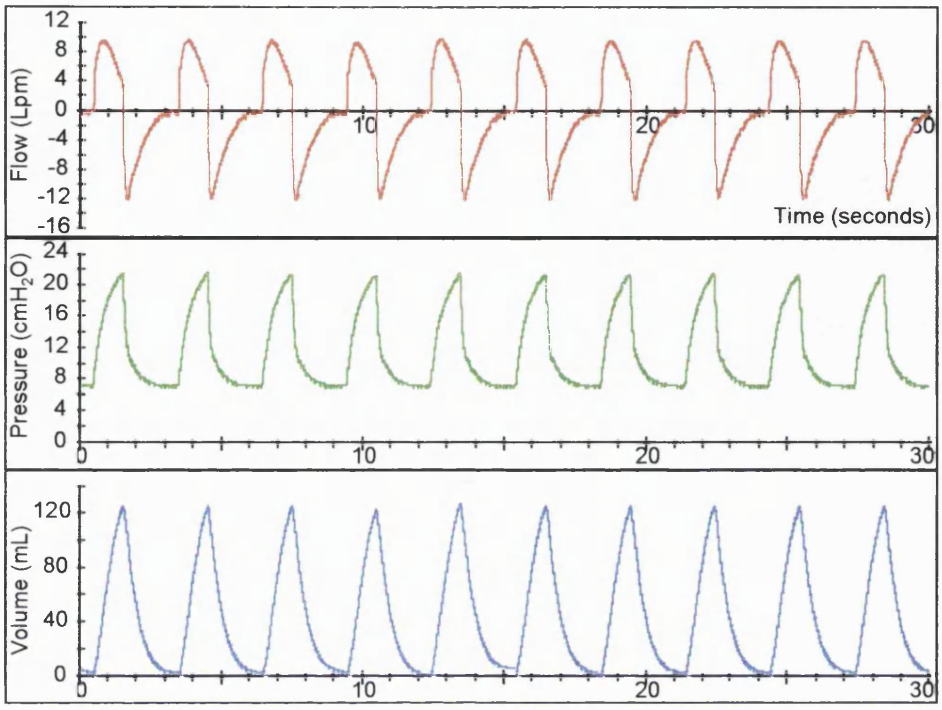
The respiratory rate (breaths/min) was calculated by the "CO_2SMO Plus" from the flow-time tracing (Figure 2-2). The beginning of each inspiration (zero flow) was used as the identification point for each breath, so that the duration of each breath (t_{TOT}) could be measured and respiratory frequency was expressed in breaths per minute (Equation 2-1).

Equation 2-1

$$Respiratory\ Rate = \frac{1}{t_{TOT}} X\ 60$$

The average respiratory rate was computed over an 8 breath moving average of $60/t_{TOT}$ and updated breath by breath.

Figure 2-2: Flow, pressure and volume traces plotted against time



The respiratory rate was automatically calculated from the flow-time tracing (in red), while PEEP, PIP and MAP were measured or calculated from the pressure-time plot (in green). Volumes (in blue) were integrated from flow and time.

Peak inspiratory pressure (PIP) was measured from the pressure-time plot (Figure 2-2) and was derived from the highest absolute pressure data point during the inspiratory phase. Mean airway pressure (MAP) was the average pressure in the airway during a complete breath. The value was calculated as the average of all data pressure points during a respiratory cycle. Positive end expiratory pressure (PEEP) was the positive pressure maintained at the end of expiration. PIP, MAP and PEEP were all expressed in cmH_20 (1 cmH_2O = 0.098 kPa).

Volumes were derived from the integration of flow with respect to time and minute ventilation (MV) was an expression of volume per minute which was calculated from tidal volume (V_T) multiplied by the respiratory rate. V_T expressed per kg body weight was automatically calculated by "CO_2SMO Plus" when the weight of the patient was entered. Tracheal tube leaks could be identified by a difference in magnitude between V_{TI} and V_{TE} and were commonly encountered in the paediatric intensive care unit where uncuffed tracheal tubes were routinely used. Unfortunately, magnitude of tracheal tube leak was not automatically calculated by the "CO_2SMO Plus" and was calculated during

analysis of each subject from raw V_{TI} and V_{TE} data (Equation 5-1). Because of the potential for tracheal tube leak to result in a gross overestimation of V_{TI} but less underestimation of V_{TE}, V_{TE} was considered to be more accurate and preferable for calculations of V_T/kg, $V_{D_{phys}}$/ V_T, VCO_2, MV and other derived respiratory parameters (Kuo et al. 1996).

2.2 Respiratory mechanics

The simultaneous measurement of flow and pressure by the "CO_2SMO Plus" facilitated the automatic calculation of the dynamic mechanical properties of the respiratory system (R_{rs} and C_{rs}) (MacNaughton, 1997). Several methods have traditionally been used to calculate dynamic C_{rs} and R_{rs} including the Mead-Whittenberger technique (Mead and Whittenberger, 1953), Least-Squares analysis and multiple linear regression. (Davis et al. 1996). The "CO_2SMO Plus" provided calculations of C_{rs} using both the Mead-Whittenberger technique and Least-Squares analysis, while calculating R_{rs} by Least-Squares analysis alone.

Measurements of C_{rs} and R_{rs} with the "CO_2SMO Plus" were not valid except in the absence of respiratory muscle activity. When assisted ventilation was augmented with spontaneous breaths, pressure changes at the airway opening were distorted by the combination of muscular effort by the patient and pressure delivery by the ventilator, and no longer reflected the underlying respiratory mechanics. Subjects were only eligible for this study if they were paralysed or deeply sedated so that no spontaneous breaths occurred and so that measurements reasonably reflected underlying R_{rs} and C_{rs}. Several authors have found that accurate measures of C_{rs} could be obtained as long as patients were relaxed and not making spontaneous respiratory efforts. Paralysis was not essential if sedation was adequate (Conti et al. 1995; Iotti et al. 1995).

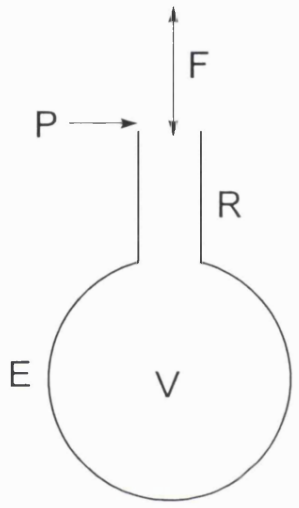
Compliance (C_{rs}) expressed in mL/cmH_2O is a measure of the distensibility or elasticity of the respiratory system and refers to the ratio of change in volume to change in pressure over the respiratory cycle. Thus, if the lung inflates easily the lung is compliant, whereas if the lung needs high pressures to inflate it, it is stiff or non-compliant (Widdicombe and Davies, 1991). C_{rs} is determined by the relationship between the inward elastic recoil of the lungs and the outward elastic recoil of the chest wall. The

soft bones of the infant rib cage mean that the elastic recoil of the thorax is very low (Papastamelos et al. 1995). Therefore the force opposing pulmonary elastic recoil is small (Phelan et al. 1982). As the chest wall contributes little to the performance of the respiratory system in new-born infants, the properties of the lungs can be approximated by measurements over the whole respiratory system. The compliance of the chest wall decreases after approximately 6 months of age with the development of muscles, rib ossification and the stiffening of the chest wall (Motoyama and Davis, 1990).
Respiratory system compliance (C_{rs}) depends on numerous factors including delivered V_T, FRC, lung water content, tissue elasticity, surfactant action, pulmonary blood flow and volume and the visco-elastic properties of the respiratory system (Fletcher M et al. 1990; Fletcher M et al. 1991; Hjalmarson, 1994).
Respiratory system resistance (R_{rs}), expressed in $cmH_2O/L/s$, is defined as the pressure required to move gas at a flow of 1L/s. It is defined by the combination of airway resistance and tissue resistance. R_{rs} decreases with age as airway calibre increases with growth. Airway calibre may additionally be influenced by bronchial smooth muscle tone, mucosal oedema, scar tissue, secretions or thickening of the airway wall due to muscle hypertrophy or stenosis, as well as the presence of a tracheal tube (Hatch and Fletcher, 1992). Since airway resistance is proportional to the fourth power of the radius of the airway, even small changes in calibre can lead to marked changes in airway resistance. In intubated patients the tracheal tube offers a significant resistance to flow and makes it hard to obtain a leak proof seal. The characteristics and size of a tracheal tube will influence the passage of air and resistance to air flow through it (Manczur et al. 2000). Tidal volume has been shown to decrease slightly and R_{rs} increase when a smaller diameter tracheal tube is used (Farstad and Bratlid, 1991). The same authors also reported increased V_T and peak airflow through the tracheal tube if the peak inspiratory pressure (PIP) was increased which resulted in a decreased C_{rs} and an increased R_{rs}. R_{rs}, or its reciprocal 'conductance', has the potential to provide information about the large airways while C_{rs} or its reciprocal 'elastance' will describe the conditions that affect the recoil of the lungs in infants (Hjalmarson, 1994).

Most methods for calculating C_{rs} and R_{rs} assume that the lung is a single compartment model which can be described by a linear differential equation (Equation 2-2). The single compartment model likens the respiratory system to a balloon on a pipe (Figure 2-3).

The model has only two variables that describe the properties of the respiratory system: the elastance (E) of the balloon and the resistance (R) of the pipe. C_{rs} and R_{rs} may be estimated either by applying linear regression analysis after sampling of concomitant pressure and flow data over any part or the whole of a breath, or by using zero flow and mid volume data points only (Krieger, 1963).

Figure 2-3: Single compartment lung model



E is the elastance of the balloon (respiratory system), R is the resistance of the system and F is the flow at the model opening. V represents the volume and P the pressure.

The single compartment lung model is based on the theory that if the model is inflated and empties passively, the relationship between the pressure (P) and volume (V) in the system is described by the Equation of Motion (Equation 2-2).

Equation 2-2

$$P = \frac{1}{C}V + RF + K$$

Where 1/C is the elastance of the lung, R is the resistance of the airway and F is the flow at the model opening. The equation of motion for a linear single compartment model includes an inertive term (K) which is considered to be negligible under most conditions and is therefore ignored. During mechanical ventilation however, positive end expiratory pressure may be set which must be included in the equation as the constant K.

Commonly used techniques for calculating C_{rs} and R_{rs} (based on the single compartment lung model) include the Mead and Whittenberger's method (C_{2pt}), Linear Regression

Analysis and the Least-squares method (Sly et al. 1996). The latter two methods utilise all data points during the breath cycle for calculation. The Mead and Whittenberger method uses only the points of zero flow to calculate C_{rs} and mid volume data points to calculate R_{rs} during the respiratory cycle (Krieger, 1963). The "CO_2SMO Plus" provided calculations of C_{rs} using both the Least-squares method (C_{dyn}: Equation 2-4) and zero flow points (C_{2pt}). The "CO_2SMO Plus" calculated R_{rs} separately for the inspiratory and expiratory limbs of the respiratory cycle using the Least-squares method. This method minimised the sum of squares between the observed pressure and the best fit curve, which resulted in expressions for R_{rs} and C_{rs} consisting of cross products of volume, flow and pressure (Equation 2-4 and Equation 2-5).

The methods for measuring R_{rs} and C_{rs} have all been shown to be reasonably accurate under ideal conditions. Although C_{rs} and R_{rs} are now quite commonly calculated using the flow and pressure transducers incorporated into modern mechanical ventilators, several authors have referred to potential problems related to the interpretation of these parameters. Kuo et al. found that certain factors such as tracheal tube leak adversely influence the accuracy of each algorithm differently with some methods remaining relatively robust in the presence of a leak (linear regression analysis) and others becoming grossly inaccurate (C_{2pt}) (Kuo et al. 1996). The performance of the Least-squares method in relation to the other methods has not been assessed but its accuracy in the presence of leak will be discussed in 5.2.1. Other authors have cited inadequate sampling frequency, time lag, contaminant electrical frequencies in the intensive care unit environment and the Bernoulli effect in lateral port sampling as factors which adversely affect accuracy of respiratory mechanics calculations (Sly et al. 1996; MacNaughton, 1997).

2.2.1 Respiratory compliance

The "CO_2SMO Plus" calculated C_{dyn} by the Least-Squares method (Equation 2-3) which minimised the summed squared difference between the observed pressure (Po) and the best fit curve (Pb), using all the data points on the pressure/volume plot during the respiratory cycle. This was done by summing the square of the difference between all observed points in the actual pressure waveform and a best fit curve (Pb - Po), which resulted in the equation:

Equation 2-3

$$S = \Sigma (Pb - Po)^2 = \Sigma (Pb - (\frac{1}{C}V + RF))^2$$

Where S is the summed squared difference between the observed pressure (Po: pressure drop at the airway opening) and the pressure of the best fit curve curve (Pb), V is the volume, R is the resistance of the airway, C is the compliance and F is the flow at the model opening.

From Equation 2-3, solutions for R and C can be found (Equation 2-4 and Equation 2-5), which were continuously computed by the "CO_2SMO Plus" during respiratory monitoring.

Equation 2-4:

$$C = \frac{\sum V^2}{\sum PV - R\sum VF}$$

Where V is the volume, P is the pressure drop at the airway opening (PIP - PEEP), R is the resistance of the airway and F is the flow at the model opening. The points of zero flow during the breath cycle are excluded from the calculation.

2.2.2 Respiratory Resistance.

R_{rs} was derived separately by the "CO_2SMO Plus" for both the inspiratory or expiratory portion of the breath. In this study expired resistance, calculated from raw data (V, F and P) on the expiratory limb of each breath cycle, was of specific interest because it utilised the passive expiratory cycle and thus potentially provided more clinically important information about the condition of the large airways in patients and less about the ventilator (Hjalmarson, 1994). In addition, the expiratory limb of the breath cycle was less likely to suffer from the confounding influence of tracheal tube leak. The Least-squares method employed by the "CO_2SMO Plus" to calculate expired respiratory resistance is derived from differentiation of Equation 2-3.

Equation 2-5:

$$R = \frac{\sum V^2 \sum PF - \sum PV \sum FV}{\sum V^2 \sum F^2 - (\sum VF)^2}$$

Where V is the volume, P is the pressure drop at the airway opening (PIP - PEEP), R is the resistance of the airway and F is the flow at the model opening. The points of zero flow during the breath cycle are excluded from the calculation.

2.3 CO_2 monitoring

Carbon dioxide (CO_2) is produced by the body as a by-product of the total cellular metabolic process. The lungs are the primary organs for excretion of CO_2 from the body. During normal conditions, the lungs excrete CO_2 at the same rate as the body produces it and there will be no net change in body CO_2 stores. Under abnormal conditions (disease, mechanical ventilation) the elimination of CO_2 (VCO_2) may be compromised by pulmonary perfusion, diffusion across the blood-gas barrier or hypo-ventilation. When this occurs, the increase in metabolic CO_2 is reflected by a rise in $PaCO_2$.

The "CO_2SMO Plus" respiratory monitor included a mainstream infrared absorption capnograph with a solid state sensor. This allowed breath by breath analysis of the concentration of CO_2 in the expired breath. Infrared capnometry is based on the principle that CO_2 absorbs light in the infrared band. An infrared beam is therefore directed through the gas sample, and the absorption of light by the molecules in the sample is measured. The amount of light absorbed is proportional to the concentration of CO_2 in the sample.

2.3.1 $ETCO_2$

CO_2 concentration in the expired breath, expressed in kPa, was calculated by the "CO_2SMO Plus" as an 80 ms moving average of the expiratory CO_2 samples and the largest average value over the expiratory interval was reported as the $ETCO_2$. The mainstream sampling and direct connection of the sensor to the tracheal tube were both

factors likely to improve accuracy of CO_2 measurements. The plot of CO_2 concentration in the expired breath against expired volume results in the $SBCO_2$ plot (Figure 2-5).

2.3.2 VCO_2

The volume of CO_2 eliminated per minute (VCO_2), expressed in mL/min, is the net volume of expired CO_2 measured at the mouth over each minute. Carbon dioxide elimination (VCO_2) corresponds to the metabolic rate during steady state. Any transient change in ventilation, perfusion, or V/Q ratio will be reflected in a transient change in VCO_2 after which a new steady state is established (Taskar et al. 1995). CO_2 elimination from the lung depends almost exclusively on alveolar ventilation. $PaCO_2$ depends on CO_2 production and alveolar ventilation (Sly et al. 1996).

CO_2 volume per breath was calculated by the "CO_2SMO Plus" by summing the product of the CO_2 percentage and V_T samples over the whole breath. VCO_2 was then calculated as the average of the CO_2 volumes per breath over one minute. The inspired CO_2 volume (negligible) was then subtracted from the total CO_2 volume to yield the expired CO_2 volume. Due to the complex interaction between V_T, $V_{D_{phys}}$ and alveolar ventilation the volume of CO_2 excreted in each breath is variable. The option of selecting averaging intervals of 8 breaths or 1, 3, 5 or 10 minutes was available to the user so that the effect of normal breath to breath changes in CO_2 volume was decreased. For this study the 8 breath averaging interval was selected. VCO_2 /kg was automatically calculated by the "CO_2SMO Plus" if patient weight was entered. The validity of VCO_2 calculations can be adversely affected by leaks in the collecting system such as pneumothorax, broncho-pleural fistulae or tracheal tube leak. In these circumstances, values may not accurately reflect the underlying physiology.

2.3.3 $PeCO_2$

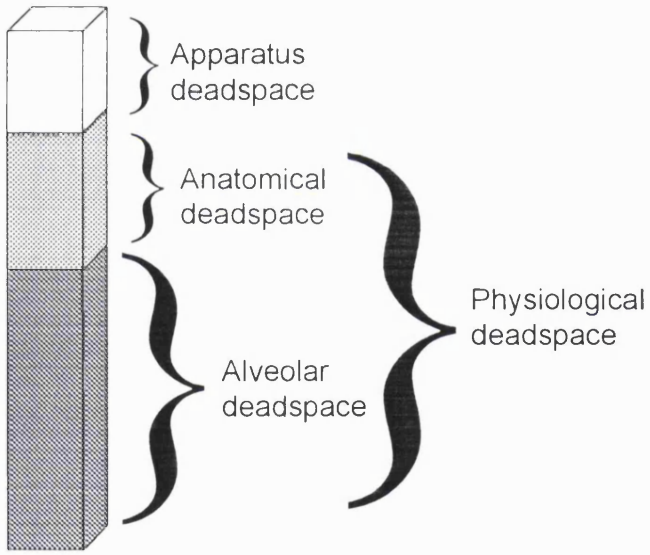
Mixed Expired CO_2 ($PeCO_2$) expressed in kPa is the partial pressure of CO_2 in the expired gas. The fraction of expired CO_2 ($FeCO_2$) was calculated by the "CO_2SMO Plus" by dividing the VCO_2 per breath by the 8 breath average of V_{TE}. The $FeCO_2$ was then converted into partial pressure by multiplication with barometric pressure minus vapour pressure. Deadspace has the effect of diluting the CO_2 content of expired air below the alveolar level. Since the body needs to expire a certain volume of CO_2 per

minute, the effect of a low $PeCO_2$ is to require more total ventilation to maintain homeostasis.

2.4 Respiratory deadspace and single breath CO_2 ($SBCO_2$) analysis

The term respiratory or total deadspace refers to the volume of each breath that is inhaled but does not participate in gas exchange. It usually consists of three components: apparatus deadspace, anatomical deadspace and alveolar deadspace (Figure 2-4). Physiological deadspace refers to the sum of alveolar and anatomical deadspace. The volume of deadspace measured depends on the method of measurement, tidal volumes, the posture of the child, whether or not they are intubated and whether they are breathing spontaneously or have assisted ventilation.

Figure 2-4: Respiratory deadspace



2.4.1 Apparatus deadspace

Apparatus deadspace (mL) refers to the deadspace introduced by the breathing circuit used for mechanical ventilation (tracheal tube and connections proximal to the equipment for measuring deadspace). This volume is often treated as an extension of anatomical deadspace, a convention that is followed in the calculations of the "CO_2SMO Plus". Since the flowmeter is connected to a variable length of tracheal tube, the "anatomical" deadspace measured by the "CO_2SMO Plus" includes the deadspace of the tracheal tube and connection. By contrast, the true anatomical deadspace is reduced

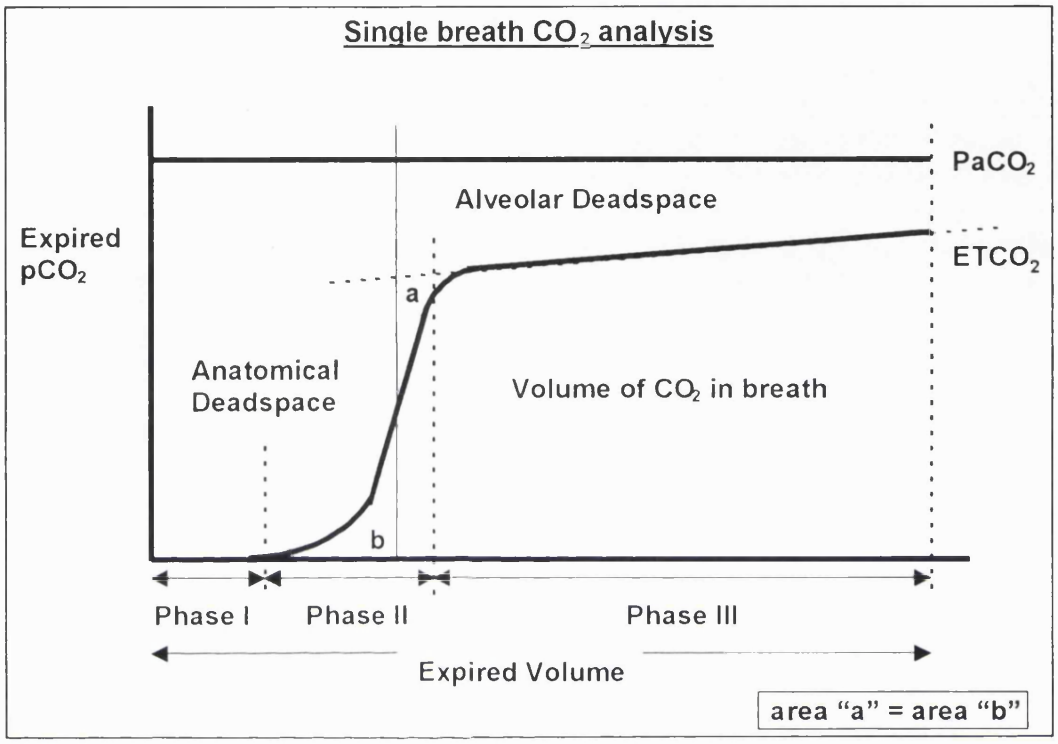
during mechanical ventilation since the conducting areas of the nasopharynx are bypassed by the tracheal tube. The apparatus deadspace subtracted from the measured anatomical deadspace would yield the volume of the anatomical deadspace (excluding the conducting areas of the nasopharynx). Because the purpose of this study was to evaluate the effect of therapeutic interventions, no effort was made to measure or subtract the apparatus deadspace from the anatomical deadspace since it remained constant throughout the measurement period.

2.4.2 Anatomical deadspace ($V_{D_{airway}}$)

Anatomical deadspace ($V_{D_{airway}}$) is defined as extending from the airway opening to the interface between inspired and alveolar gas. Its volume is that of all the conducting airways and naso-pharynx and is difficult both to identify anatomically and to measure. One way of measuring $V_{D_{airway}}$ is to calculate physiological deadspace ($V_{D_{phys}}$) from the Bohr equation (Equation 2-9). In normal subjects $V_{D_{airway}}$ is almost equal to the $V_{D_{phys}}$. However this assumption is not true in patients with lung disease in whom $V_{D_{phys}}$ can be considerably larger than $V_{D_{airway}}$ (Widdicombe, 1974; West, 1995).

The use of expired CO_2 analysis to measure respiratory deadspace was introduced by Aitken and Clarke-Kennedy in 1928. Fowler developed a functional method of measuring $V_{D_{airway}}$ which involved plotting the concentration of N_2 in expired gas against expired volume during a washout procedure (Fowler, 1948). Fletcher et al then adapted the technique to use expired CO_2 concentration plotted against expired volume (Fletcher (a), 1984; Fletcher (a), 1986). The "CO_2SMO Plus" simultaneously measured CO_2 and flow during expiration from which a plot of expired CO_2 versus volume could be generated. This plot known as single breath CO_2 ($SBCO_2$) or volumetric capnography was used to estimate a number of respiratory parameters such as VCO_2, $V_{D_{airway}}$, $V_{D_{alv}}$ and alveolar tidal volume (Figure 2-5)

Figure 2-5: Three Phases of Single Breath CO_2 Curve

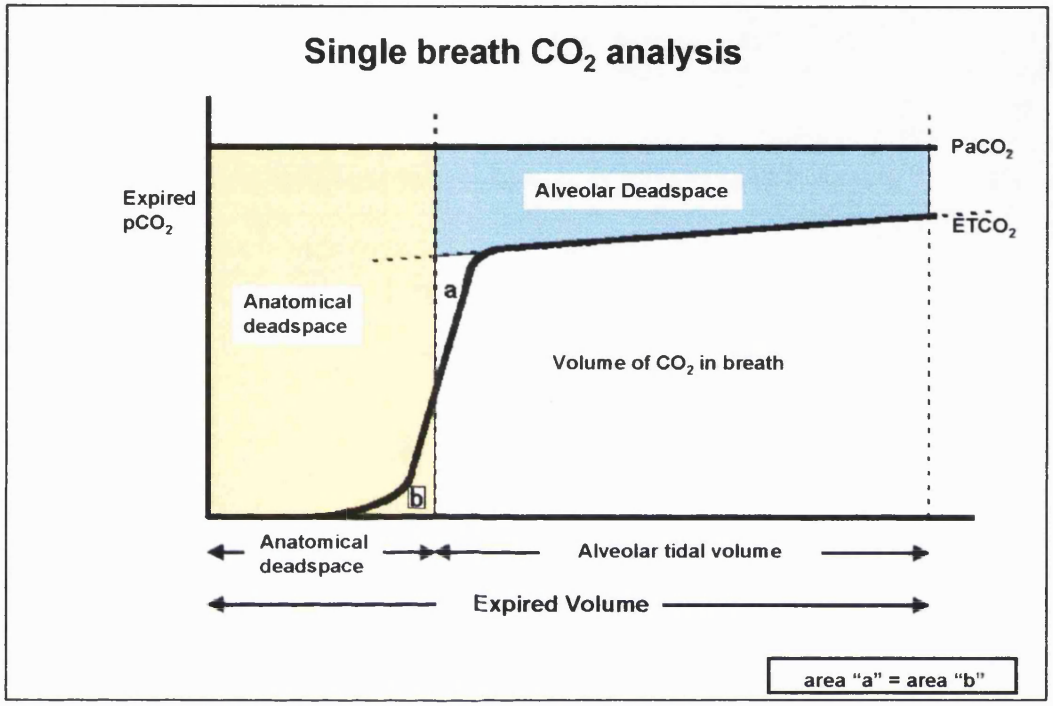


In 1950 Fowler suggested the division of the $SBCO_2$ curve into 3 distinct phases each of which was related to anatomical compartments of the respiratory system (Figure 2-5). Phase I is the volume of the proximal conducting airways which contains negligible amounts of CO_2. Phase II is the volume of the transitional region between alveolar gas and the conducting airways, characterised by a sharp increase in CO_2 concentration as gas from the alveoli mixes with gas from the conducting airways. Phase III primarily contains gas from alveoli and provides most of the expired CO_2 volume. It is characterised by a gently increasing slope, which should plateau in health. An increase in phase III slope can indicate ventilation inhomogeneity.

$V_{D_{airway}}$ also known as Fowler's deadspace, was calculated by the "CO_2SMO Plus" using this method. This functional measurement of $V_{D_{airway}}$ is the volume of conducting airways at the midpoint of the CO_2 concentration transition between conducting airways and alveolar gas (Figure 2-6). The extrapolated phase III slope was used to determine the point at which volumes of CO_2 represented by areas a and b were equal. The slope of phase III was computed by linear regression of the points bounded by 30% to 70% of

expired CO_2 volume. The proportions of expired volume contributed by anatomical deadspace and alveolar tidal volume are thus shown in Figure 2-6.

Figure 2-6: Volumetric Capnography



In normal adults, this $V_{D_{airway}}$ equates to approximately 150 ml (2.2ml/kg), but can be up to 3.3ml/kg in neonates (Numa and Newth, 1996). Leakage from the ventilator tubes will tend to produce an underestimation of $V_{D_{airway}}$. For a given alveolar ventilation, increasing V_T and decreasing respiratory rate or vice versa does not affect $V_{D_{airway}}$ in adults or children. In addition, $V_{D_{airway}}$ is relatively constant during undisturbed anaesthesia but lateral turns, sternotomy or thoracotomy may have significant effects on the magnitude of airway deadspace (Fletcher and Jonson, 1984).

2.4.3 Alveolar deadspace ($V_{D_{alv}}$)

Alveolar deadspace ($V_{D_{alv}}$), also referred to as wasted ventilation, is the volume of gas that moves into functional gas exchange units but does not take part in gas exchange because of unperfused alveoli. Wasted ventilation includes both gas in completely unperfused alveoli as well as a portion of the gas in poorly perfused alveoli. As with $V_{D_{airway}}$, this area is anatomically difficult to identify or measure. A reasonable approximation of $V_{D_{alv}}$ can be calculated by subtracting $V_{D_{airway}}$ volume (calculated by the modified Fowlers method) from $V_{D_{phys}}$ (calculated by the modified Bohr equation).

This was the method utilised by the "CO_2SMO Plus" to calculate $V_{D_{alv}}$. The derivation of the Bohr equation is discussed in 2.4.4.

Oxygen uptake depends on the matching between alveolar ventilation and pulmonary perfusion (V/Q matching) and on diffusion time, diffusion gradient and diffusion area (Poets and Martin, 1996). $V_{D_{alv}}/V_T$ reflects the degree to which alveolar ventilation and perfusion fail to match each other, whether regionally in the lung as in pulmonary embolism or globally as in asthma.

Wasted ventilation may occur due to any condition that abnormally elevates the ventilation/perfusion (V/Q) ratio such as pulmonary hypotension, pulmonary embolus, hyperventilation, obstruction of pulmonary arterioles and alveolar hyperinflation. In children both gross hypo- and hyper-perfusion cause an increase in $V_{D_{alv}}$ (Fletcher and Jonson, 1984). $V_{D_{alv}}$ increases with age with the growth of the gas exchange surface.

2.4.4 Physiological deadspace ($V_{D_{phys}}$)

Physiological deadspace ($V_{D_{phys}}$) refers to the sum of $V_{D_{alv}}$ and $V_{D_{airway}}$. Once again, however, $V_{D_{phys}}$ is not an identifiable anatomical volume and the methods that measure it are based on functional definitions of deadspace rather than morphological definitions. The "CO_2SMO Plus" calculated $V_{D_{phys}}$ and alveolar deadspace ($V_{D_{alv}}$) using a modified version of the Bohr equation developed by Christian Bohr in 1891. The theoretical basis for the Bohr equation is that the volume of CO_2 in a breath collected at the mouth is equivalent to the volume expired from the functional alveolar space. The total amount of a gas in an expired breath is the volume of that gas times its fractional concentration. Because CO_2 in the expired gas must have come from alveolar ventilation:

Equation 2-6: $$\mathbf{VCO_2 = V_T F_E CO_2}$$

where V_T is the volume exhaled per minute and F_ECO_2 is the fractional concentration of CO_2 in mixed expired gas. Since the expired volume (V_T) consists of both deadspace and the expired alveolar volume, Equation 2-6 can be rearranged:

Equation 2-7: $$\mathbf{V_T F_E CO_2 = (V_T - V_D) F_A CO_2 + V_D \times 0}$$

where F_ACO_2 is the fractional concentration of CO_2 in the alveolar space. The concentration of CO_2 in the deadspace is assumed to be zero. Now Equation 2-7 is rearranged:

Equation 2-8: $V_DF_ACO_2 = V_TF_ACO_2 - V_TF_ECO2$

Then

Equation 2-9: $V_D/V_T = (F_ACO_2 - F_ECO_2) / F_ACO_2$

Then converting the fractional concentrations to partial pressure:

Equation 2-10: $V_D/V_T = (P_ACO_2 - P_ECO_2) / P_ACO_2$

This is the modified version of the Bohr equation for CO_2. Enghoff further modified this equation (Nunn, 1989) by suggesting that ideal alveoli have P_ACO_2 equal to $PaCO_2$ in normal subjects and that the measured arterial blood gas can be used to replace P_ACO_2:

Equation 2-11: $V_D/V_T = (PaCO_2 - P_ECO_2) / PaCO_2$

P_ECO_2 ($PeCO_2$) was calculated by the "CO_2SMO Plus" from the concentration of CO_2 in expired gas and $PaCO_2$ was obtained from simultaneous blood gas analysis. V_D/V_T is sometimes referred to as the wasted fraction of each breath. It is typically 0.33 in normal adults but can be higher (0.44 - 0.47) in neonates (Numa and Newth, 1996). V_{Dphys} may increase with lung disease because of V/Q mismatching (Hlastala and Berger, 1996). An increase in delivered V_T in a ventilated child would result in a progressive decrease in V_D/V_T. Multiplying the V_D/V_T by V_T gives the total volume of deadspace. The volume of air in the tracheal tube, connector and tubing proximal to the CO_2 measurement will contribute to this volume. V_{Dphys} is obtained when $V_{Dairway}$ is subtracted from total deadspace volume.

2.5 Arterial blood gases

Arterial blood gases are the gold standard for monitoring changes in respiratory function in ventilated children. The portable bedside system used for analysis of blood gases in the intensive care units at Great Ormond Street Hospital was the Hewlett Packard i-Stat Blood Analysis System. The system analyses arterial blood gases when a cartridge filled with a patient's arterial blood sample is inserted into a hand held analyser. A capillary chamber draws the sample into the cartridge. Calibrant is drawn from a gas-tight sealed

pouch to the sensors and electrochemical measurements are made on the calibrant fluid. Then a diaphragm pump delivers the blood sample and electrochemical measurements are repeated. The i-Stat system uses miniaturised versions of standard electrochemical electrodes to perform potentiometric (voltage) and amperometric (current) measurements on solutions and relate these to the concentrations of the analytes of interest.

Each i-Stat cartridge contains sensors for the measurement of pH, $PaCO_2$ and PaO_2, heating elements, reference electrodes, sensors for the measurement of specific analytes and a buffered aqueous calibrant solution of known concentrations. The calibrant solution is buffered to pH = 7.43 which contains 30mmHg of PCO_2 and 160mmHg of PO_2 and automated internal calibration occurs daily.

An independent study comparing the performance of the i-STAT portable clinical analyser for measuring blood gases and pH to a conventional blood gas analyser (ABL520 Radiometer) found that the two systems gave nearly identical values and that blood gas analysis using the i-STAT portable device was comparable with that performed by a conventional laboratory blood gas analyser (Sediame et al. 1999).

2.5.1 pH and $PaCO_2$

$PaCO_2$ along with pH is used to assess the balance between acids and bases in the blood plasma. The ingestion and production of acidic and basic material by the body is offset by the amount of acidic and basic material metabolised and excreted. Normal blood plasma is slightly alkaline with an excess of hydroxyl ions in comparison to hydrogen. The $PaCO_2$ is a measure of the partial pressure of CO_2 dissolved in arterial blood. It represents the respiratory component of acid base balance and reflects the balance between cellular production of CO_2 and ventilatory removal of CO_2. A change in $PaCO_2$ indicates an alteration in this balance. Causes of primary respiratory acidosis (increase in $PaCO_2$) in paralysed ventilated children include airway obstruction, mechanical hypo-ventilation or acute changes in V/Q matching. Primary causes of respiratory alkalosis (decreased $PaCO_2$) include mechanical hyperventilation, acute improvement in pulmonary gaseous exchange, oedema and neurological disorders.

$PaCO_2$ and pH are measured by direct potentiometry. Potentiometric measurements measure the potential difference between the sensing electrode and a non-responding reference electrode in a solution. The concentration of pH or CO_2 are then related to potential difference through the Nernst equation.

The manufacturers compared the accuracy of pH and $PaCO_2$ measurements with the i-Stat against the accuracy of four other validated systems. The mean CV between methods was between 0.04% and 0.05% for pH and between 1.3% and 3% for $PaCO_2$. The correlation between methods exceeded 0.98 in all cases but one (where r = 0.95) for pH and exceeded 0.98 in all cases for $PaCO_2$.

2.5.2 PaO_2

PaO_2 is a measurement of the partial pressure of oxygen dissolved in arterial blood. Some causes for reduction in PaO_2 include decreased pulmonary ventilation, impaired pulmonary gas exchange, and cardiopulmonary shunting and V/Q inequality.
PaO_2 is measured amperometrically. Amperometric measurements are the steady state measurements of the current flowing through an electrode when an electrochemical reaction is occurring. The current generated at the electrode is directly proportional to the number of electrons being transferred between the electrode and the analyte in solution. Oxygen thus permeates through a gas permeable membrane from the blood sample onto an internal electrolyte solution where it is reduced at the cathode. The oxygen reduction current is proportional to the dissolved oxygen concentration.
The comparison of HP i-Stat performance in PO_2 measurements against 4 other validated systems yielded a correlation which exceeded 0.995 in all cases. The mean CV between methods was between 2.06% and 3.92%.

2.5.3 HCO_3-

Bicarbonates are inorganic salts that contain the HCO_3- radical. They are an important factor in determining the pH of the blood and the concentration of bicarbonate ions is regulated primarily by the kidneys. HCO_3- (bicarbonate) is the most abundant buffer in blood plasma and an indicator of the alkali reserve or buffering capacity of the blood. HCO_3- represents the metabolic component of acid-base balance and causes of primary metabolic acidosis (decrease in HCO_3-) include lactate acidosis (hypoxia), diarrhoea and

ketoacidosis. Causes of primary metabolic alkalosis include vomiting and alkaline treatments. HCO_3- is calculated by the following equation using measured values for pH and $PaCO_2$.

Equation 2-12

$$\log HCO_3^- = pH + \log PaCO_2 - 7.608$$

2.5.4 Base Excess

Base excess of the extracellular fluid or standard base excess is defined as the concentration of titratable base minus the concentration of titratable acid when titrating the average intracellular fluid to an arterial plasma pH of 7.4 at $PaCO_2$ of 40mmHg at 37°C. Excess concentration of base in the average extracellular fluid remains virtually constant during acute changes in $PaCO_2$ and reflects only the non respiratory component of pH disturbances. Base excess is calculated by the following equation using the measured pH and calculated HCO_3-.

Equation 2-13

$$BE_{ecf} = HCO_3 - 24.8 + 16.2(pH - 7.4)$$

2.5.5 SaO_2

SaO_2 or oxygen saturation is the amount of oxyhaemoglobin expressed as a fraction of the total amount of haemoglobin able to bind oxygen (oxy- plus deoxyhaemoglobin). SaO_2 is calculated from measured PaO_2, $PaCO_2$ and pH. This calculation assumes normal affinity of oxygen for haemoglobin and assumes that normal amounts of dysfunctional haemoglobin are present. SaO_2 is a useful predictor o f the amount of oxygen that is available for tissue perfusion. Reduced levels of SaO_2 may be caused by low PaO_2 or impaired ability of haemoglobin to carry oxygen.

2.5.6 Factors affecting results

Exposing the arterial blood sample to air allows CO_2 to escape which causes $PaCO_2$ to decrease, pH to increase and HCO_3- to be under-estimated. In addition PaO_2 will increase when values are below 150mmHg or decrease when values are above 150mmHg. Allowing blood to stand (without exposure to air) before testing allows $PaCO_2$ to increase and pH to decrease due to metabolic processes which causes HCO_3- to be overestimated. Thus changes in the measured pH and $PaCO_2$ affect the calculated

values. SaO_2 values calculated from measured $PaCO_2$ and an assumed oxyhaemoglobin dissociation curve may differ significantly from the direct measurement.

3. Validation of equipment

3.1 Validation of the "CO_2SMO Plus"

The manufacturers printed specifications relating to the "CO_2SMO Plus" (Novametrix Medical Systems inc. Wallingford, CT) suggested that the accuracy, linearity, dead space, resistance and frequency response of the instrument were suitable for the purposes of this research. However, these investigations were not performed in clinical environments and did not take into account the potential effects of adding a tracheal tube to the flow meter circuit. Addition of a tracheal tube may cause significant degradation of the linear range over which the flow meter is accurate (Jackson et al. (b) 1995). In addition a wide variety of algorithms are used in the "CO_2SMO Plus" software, some of which have underlying assumptions that may not be valid when applied to measurements in ventilated infants. Further *in vitro* studies were therefore performed to identify potential hardware and software problems. *In-vivo* studies were also necessary to determine the effects of tracheal tube leaks, appropriate measurement intervals for obtaining baseline and post-treatment data, normal variability of parameters in the absence of intervention, and the effects of connection and disconnection of the flow sensor. These could not be accurately assessed *in-vitro* (Jackson et al. (b) 1995).

3.1.1 Accuracy of volume (flow) recordings

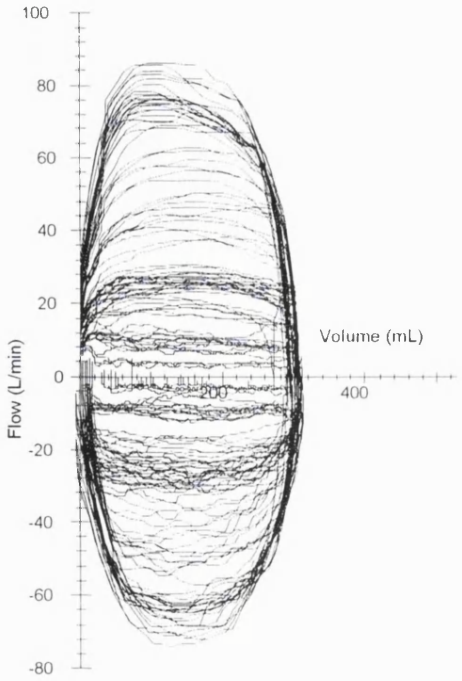
Accuracy of flow recording and linearity for the neonatal, paediatric and adult flow sensors were established by connecting each in turn to an appropriate size of calibrated Hans-Rudolf syringe. Different volumes were passed through the flow sensors at variable frequencies to establish whether flow and time were successfully integrated by the "CO_2SMO Plus" to produce an accurate reflection of the known volumes. This method had the dual advantage of assessing accuracy of volume integration as well as determining the linear range in which flow recordings were accurate. The flow range for which volume was accurately integrated was determined by the linear range of the neonatal, paediatric or adult flow sensor. Flow sensor specifications published by the manufacturers suggested that the neonatal and adult flow sensors were accurate to within 3% between flows of 0.25 to 28L/min and 2 to 180L/min respectively. The manufacturer's limits for V_T were 1 - 500mL for the neonatal flow sensor, 30 - 1000mL

for the paediatric flow sensor and 100 to 3000mL for the adult flow sensor within the stated flow range.

3.1.1.1 Methods:

1. Using Hans-Rudolph calibrated syringes, various known volumes between 2mL and 500mL, were manually pumped at variable speeds through the "CO_2SMO Plus" neonatal, paediatric and adult flow sensors for a minimum of 2 minutes (± 100 breaths), as illustrated in Figure 3-1. Variable flow was used to establish the linear range for each sensor (i.e. that range over which flow and volume could be measured to within 5% accuracy).
2. The tests were repeated using a second neonatal, paediatric and adult flow sensor to explore the variability, if any between sensors. This was not expected to be substantial since all sensors were cast in hard plastic from a single mould.
3. The tests were repeated with each of the flow sensors connected to tracheal tubes of different internal diameters (3.0 to 6.5 mm) to assess the effect of such connection on linearity in the clinical environment.

Figure 3-1: Variable flow through an adult sensor with a 300mL syringe



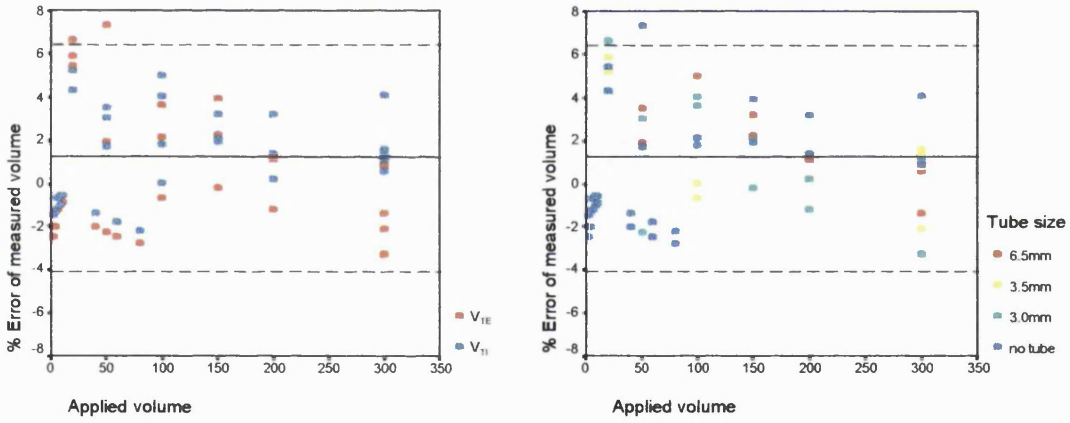
Superimposed flow volume loops generated from pushing 300mL volumes through the "CO_2SMO Plus" adult flow sensor at variable flow. It can be seen that volume integration was reasonably accurate at all but extremely low flow.

3.1.1.2 Results

3.1.1.2.1 Neonatal flow sensor

Preliminary measurements on infants during pilot studies suggested that linear flow ranges between 1.5 - 20L/min would be clinically appropriate for infants under 2 years with V_T <200mL. Therefore volumes between 2 and 300mL were passed through the neonatal flow sensor using variable flows between 0.75 and 28L/min (13-467mL/sec). Mean % error for V_{TI} and V_{TE} measurements for each of the fow sensors with and without tracheal tube attachments are shown in Figure 3-2 to Figure 3-4.
Tables with numerical details of measured volumes integrated from flow and time by the software are displayed in the Appendix (Table 10-1).

Figure 3-2: Accuracy of volume recordings with neonatal sensor



Mean difference shown by solid and 95% limits of agreement by broken lines. Percentage error was less than 8% for all recordings and there was no systematic error related either to inspiratory or expiratory volume recordings or the addition of tracheal tubes of various sizes.

The CV was always <10 % (<5% for >80% of trials) for both V_{TE} and V_{TI}. Percentage error was <8% for all volumes within the linear range of the neonatal flow sensor. From Figure 3-5, gross inaccuracies in V_T recordings occurred when flow was >28 L/min. Inaccuracies in the neonatal flow sensor were also recorded when flow was very low (<0.75 L/min).

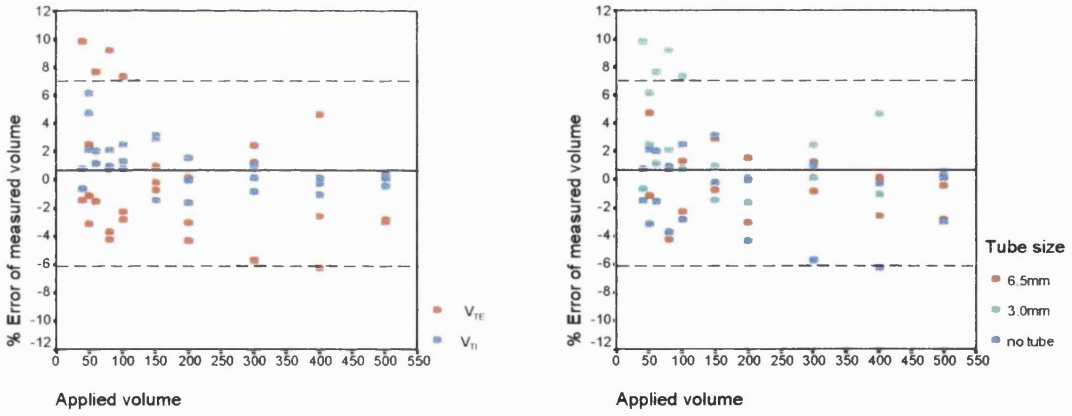
The addition of a tracheal tube to the circuit did not substantially change recorded volumes and between-sensor differences were insignificant (Figure 3-5). Volume recordings using the neonatal flow sensor were therefore considered to be very acceptable for use in the study and in general represented good accuracy for a device

with <1mL deadspace compared with other sensors such as the Bicore (Jackson et al. (a) 1995).

3.1.1.2.2 Paediatric flow sensor

When using the paediatric flow sensor, CV was also consistently <10% (<5% more than 80% of the time) for both V_{TE} and V_{TI}. Percentage error was less than 10% for all volumes within the linear range of the paediatric flow sensor. The paediatric sensor had a similar linearity to the adult sensor with inaccuracies occurring when flow was less than 10L/min (data not shown). Volumes < 40mL were not accurately measured by the paediatric flow sensor despite the statement by the manufacturers that volumes >30mL would be measurable. As with the neonatal flow sensor, the addition of a tracheal tube to the circuit did not substantially change the volumes recorded and between-sensor differences were insignificant. The paediatric flow sensor was developed late in the data collection period of this study and was rarely used for recording respiratory function.

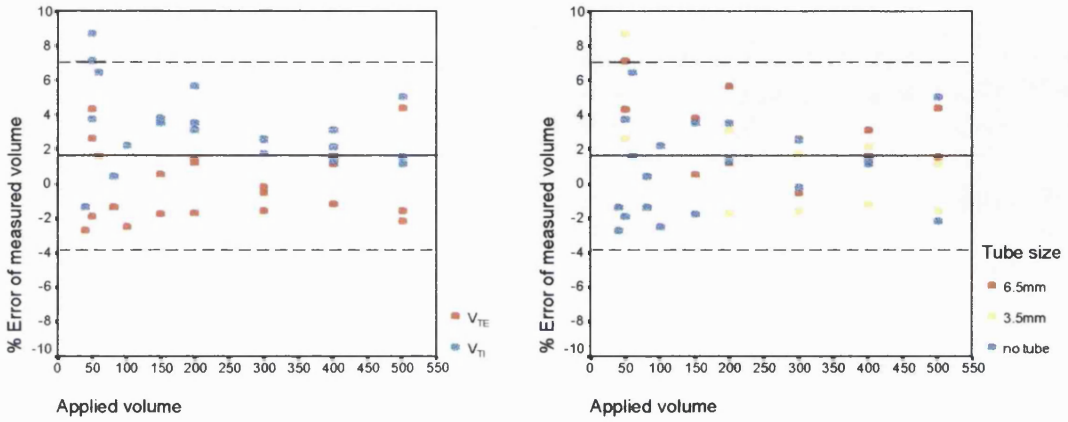
Figure 3-3: Accuracy of volume recordings with paediatric sensor



Mean difference shown by solid and 95% limits of agreement by broken lines. Data points are identical in both charts. Percentage error was <10% for all recordings and there was no systematic error related either to inspiratory or expiratory volume recordings or the addition of tracheal tubes of various sizes, although larger errors in V_{TE} were obtained when the smallest tracheal tube (3.0mm) was connected.

3.1.1.2.3 Adult flow sensor

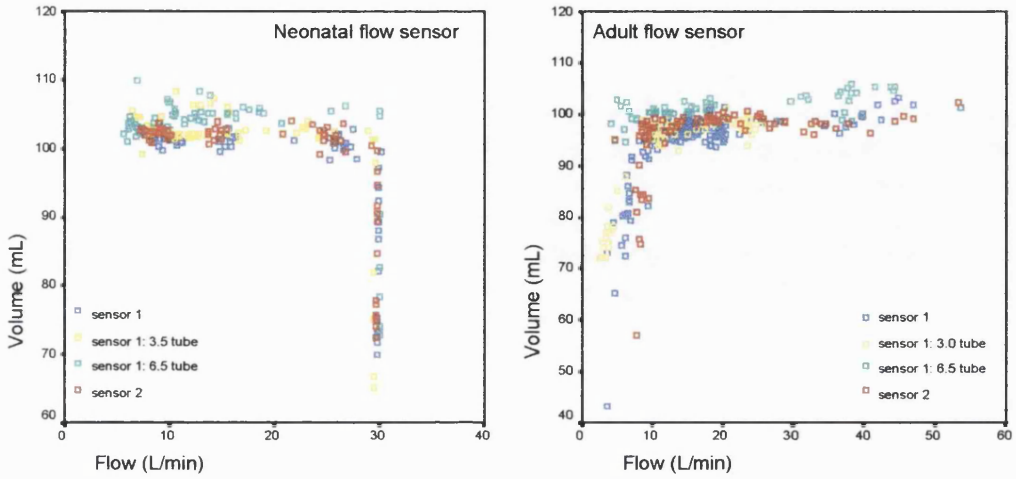
Figure 3-4: Accuracy of volume recordings with adult sensor



Mean difference shown by solid and 95% limits of agreement by broken lines. Data points are identical in both charts. Percentage error was <10% for all recordings and there was no systematic error related to the addition of tracheal tubes of various sizes. Arguably, there was a tendency for V_{TE} to be slightly underestimated and a tendency for V_{TI} to be slightly overestimated.

The adult flow sensor measured V_{TE} and V_{TI} for known volumes with CV <10%. Percentage error for V_{TE} was < 5% for all volumes and <10% for V_{TI} within the linear range of the adult flow sensor. The adult flow sensor tended to be inaccurate when flow was less than 10L/min (Figure 3-5). Volumes less than 40mL were not accurately measured by the adult flow sensor. As with the neonatal flow sensor, the addition of tracheal tubes to the circuit did not substantially change recorded volumes and between-sensor differences were insignificant.

Figure 3-5: Volume accuracy of 100mL applied signal over range of flows and measurement conditions



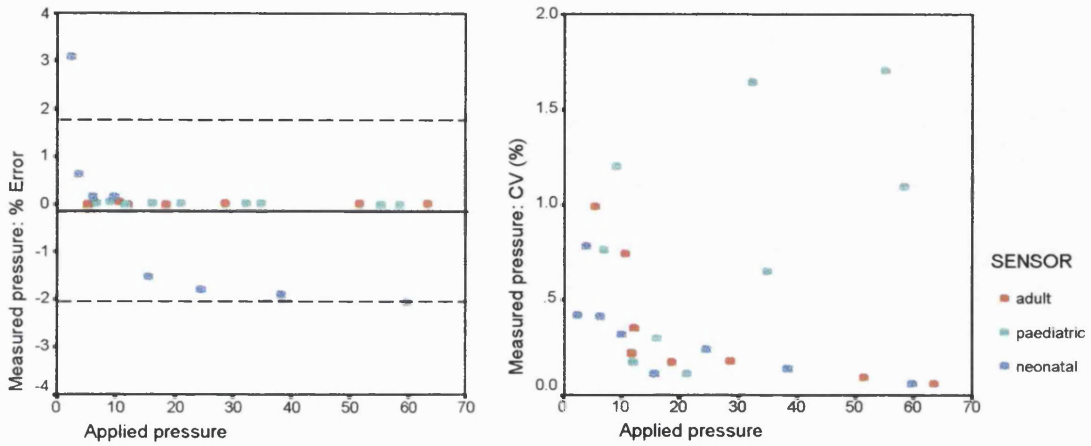
Volumes recorded by the neonatal and adult flow sensor using a 100mL Hans-Rudolph calibrated syringe. The neonatal flow sensor became inaccurate when flow exceeded 28L/min and the adult flow sensor became inaccurate when flow < 10L/min. There did not appear to be any systematic error related either to inter-sensor variability or the addition of tracheal tubes of various sizes.

3.1.2 Accuracy of pressure recordings

The accuracy of pressure recordings made by the "CO_2SMO Plus" was checked against a range of static pressures generated by a syringe and simultaneously recorded by a Digitron pressure manometer (P200UL) connected in series. The neonatal, paediatric and adult flow sensors were all checked in this fashion and the results are summarised in Figure 3-6 (and tabulated in the Appendix: 10-4). The pressure recordings by the "CO_2SMO Plus" compared favourably with those by the Digitron with < 3% error for all sensors over the pressure range assessed. The range assessed (0-70 cmH_2O) exceeded that which would be encountered clinically.

There was no drift in recordings except when there were small transient leaks in the syringe system, which were recorded by both the "CO_2SMO Plus" and the Digitron.

Figure 3-6: Percentage error and CV of measured pressure against manometer pressure



Mean difference shown by solid and 95% limits of agreement by broken lines. The percentage error was <3% for the neonatal flow sensor and <1% for the paediatric and adult flow sensors. The CV was <1% for the neonatal and adult flow sensors and <2% for the paediatric flow sensor.

The neonatal flow sensor demonstrated the greatest errors at low and high applied pressures, although these still remained less than 3%, and the CV for the neonatal flow sensor was <1%. The paediatric flow sensor demonstrated minimal error through the range of applied pressure, but had the largest CV amongst the 3 sensors. The "largest" CV remained well below 2%, indicating extremely reproducible measurements.

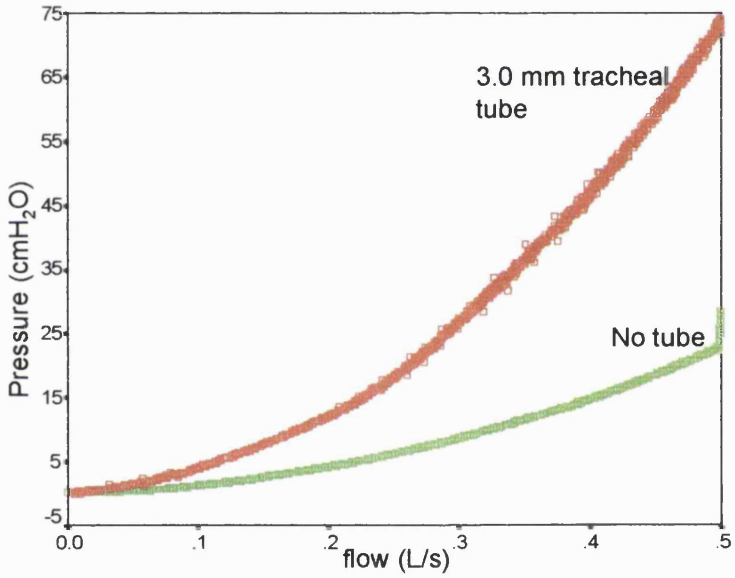
3.1.3 Pressure/flow relationships with all sensors

Having established the accuracy of flow and pressure recordings, pressure/flow and resistance/flow relationships of the sensors were investigated. Variable flows were applied through the neonatal, paediatric and adult flow sensors with and without tracheal tube connections of various sizes. This was to assess the contribution of apparatus resistance (R_{app}) to the measured resistance in clinical measurements. The design of the sensors incorporates a solid plastic mould with an inflexible internal resistance. The relationship between resistance and flow was therefore linear with resistance increasing with an increase in flow. Frey et al (2000) suggested that equipment added to the ventilator circuit should account for no more than 20% of the total R_{rs} in the ventilated child (Frey et al. (a) 2000; Frey et al. (b) 2000). Of interest therefore was the flow at which R_{app} was likely to be unacceptable.

3.1.3.1 Neonatal sensor

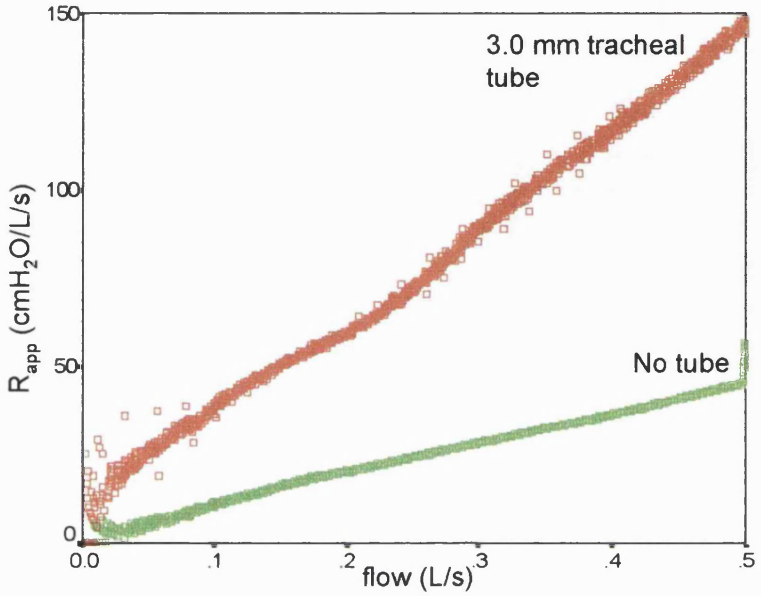
Although it can be seen from Figure 3-8 that the R_{app} was considerable (150 $cmH_2O/L/s$) at relatively high flow (0.5 L/s or 30L/min) when a 3.0 mm tracheal tube was connected, these flows were unlikely to be encountered in the clinical environment. Even at the upper limit of linear range for the neonatal sensor (30L/min), the proportion of the total R_{app} contributed by the neonatal sensor remained relatively small (50 $cmH_2O/L/s$) compared to that created by the tracheal tube.

Figure 3-7: Pressure-flow relationships of the neonatal sensor with and without 3.0mm tracheal tube attached



The pressure recorded by the neonatal flow sensor at maximal flow (0.5L/s) was more than doubled when a 3.0mm tracheal tube was connected to the circuit.

Figure 3-8: Apparatus resistance-flow relationships in the neonatal flow sensor



The relative resistive contribution of the neonatal flow sensor remained small when compared to the resistance created by the addition of a 3.0mm tracheal tube.

Table 3-1: R_{app} and R_{TT} through neonatal flow sensor

Flow (L/min)	*Flow (L/s)*	*R_{APP} (no tube) $cmH_2O/L/s$*	*R_{TT} (3.0mm) $cmH_2O/L/s$*
3.0	0.05	5.12 (0.65)	25.4 (1.22)
4.2	0.07	6.90 (0.58)	30.6 (1.24)
6.0	0.10	10.5 (0.49)	37.9 (1.51)
12.0	0.20	20.2 (0.33)	59.1 (0.59)
18.0	0.30	28.2 (0.33)	88.5 (1.18)
24.0	0.40	36.3 (0.27)	116 (1.71)
29.4	0.49	44.2 (0.17)	144 (1.29)

Results are expressed as mean (SD)

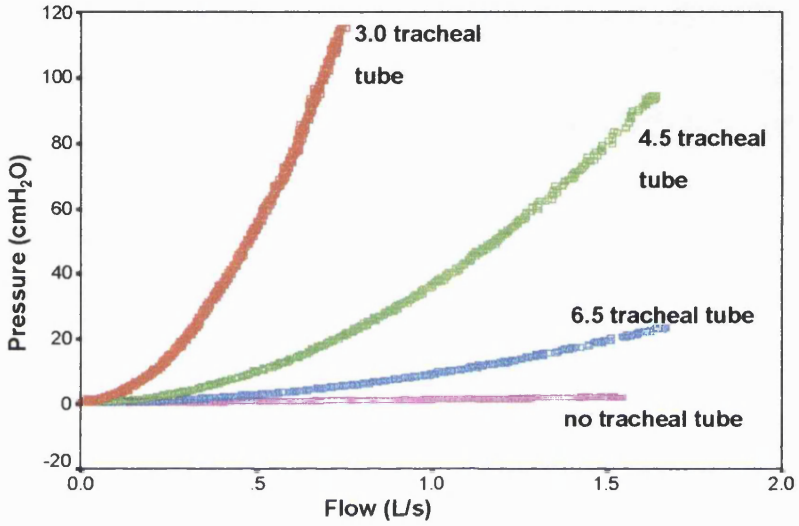
The R_{app} of the neonatal flow sensor contributed between 20 and 35% of the combined R_{app} and R_{TT} (Table 3-1), depending on the magnitude of flow. It was thus unlikely to contribute more than 20% of the total R_{rs} in the ventilated child.

3.1.3.2 Paediatric sensor

The paediatric and adult sensors contributed minimally to the total resistance in comparison to the resistance of the tracheal tubes. The clinical range of flow

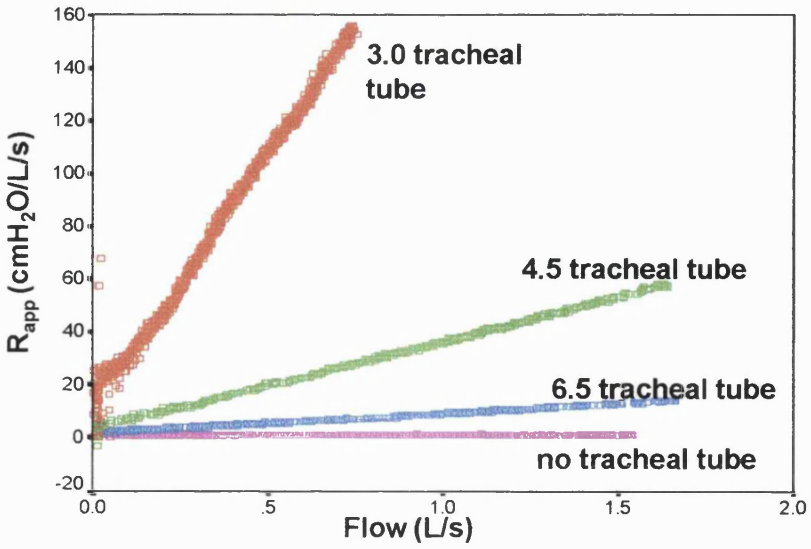
encountered in this study was much lower than the range portrayed by these charts, with peak flows rarely above 30L/min (0.5L/s).

Figure 3-9: Pressure-flow relationships of the paediatric flow sensor with various tracheal tubes attached



The pressure generated by the addition of a 3.0mm tracheal tube was excessive at flows exceeding 0.5L/s. The pressure generated by the paediatric flow sensor itself (no tracheal tube) was negligible.

Figure 3-10: Resistance-flow relationships of the paediatric flow sensor with different tracheal tube attachments



The relative resistance exerted by the paediatric flow sensor was negligible compared to the resistance exerted by the tracheal tubes. The largest resistance was generated by the smallest (3.0mm) tube.

Table 3-2: R_{app} and R_{TT} through paediatric flow sensor

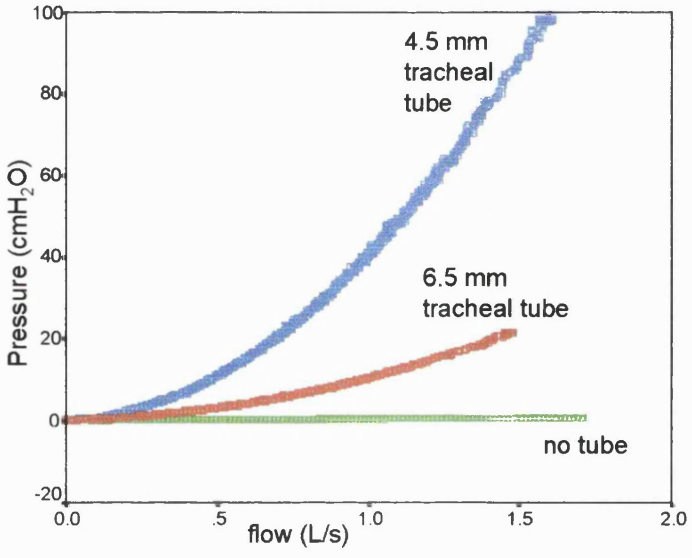
Flow (L/min)	*Flow (L/s)*	*R_{APP} (no tube) $cmH_2O/L/s$*	*R_{TT} (6.5mm) $cmH_2O/L/s$*	*R_{TT} (4.5mm) $cmH_2O/L/s$*	*R_{TT} (3.0mm) $cmH_2O/L/s$*
1.2	0.02	2.22 (0.52)			
3.0	0.05	0.98 (0.15)			
6.0	0.10	0.71 (0.32)	2.54 (0.33)	6.23 (0.52)	30.1 (1.97)
15	0.25	0.69 (0.19)	3.64 (0.08)	10.8 (0.42)	55.5 (1.41)
30	0.50	0.99 (0.05)	5.39 (0.14)	19.7 (0.53)	108.1 (1.79)
45	0.75	1.17 (0.05)	7.11 (0.12)	27.8 (0.37)	153.7 (1.33)
60	1.00	1.21 (0.04)	8.93 (0.13)	36.0 (0.32)	
75	1.25	1.25 (0.05)	10.8 (0.07)	44.4 (0.48)	
90	1.50	1.31 (0.05)	12.7 (0.13)	53.1 (0.48)	

Results are expressed as mean (SD)

The paediatric flow sensor contributed between 10 and 28% of the total R_{app} for the flow sensor and 6.5mm tracheal tube combined and considerably less for all the other tracheal tube combinations. It was therefore unlikely to contribute more than 20% to the total R_{rs} of the ventilated child.

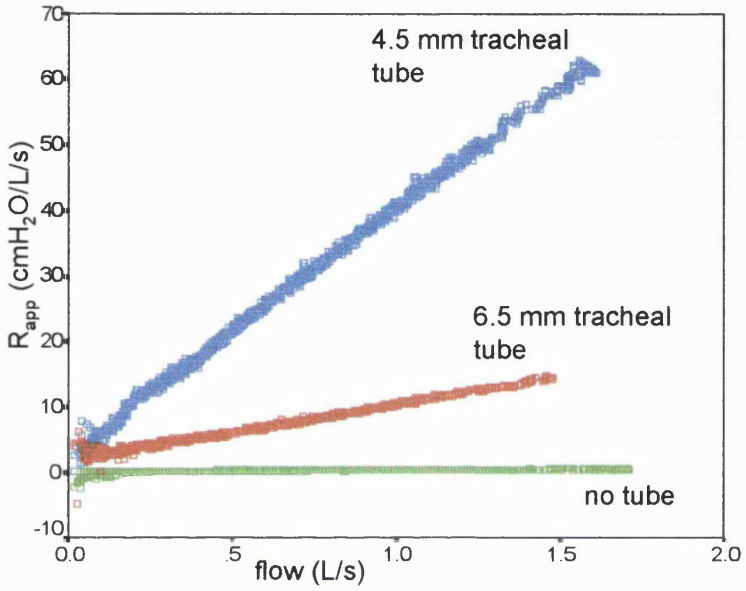
3.1.3.3 Adult sensor

Figure 3-11: Pressure-flow relationships of the adult flow sensor with different tracheal tube attachments



The pressure generated by the adult flow sensor (no tube) was negligible compared with the pressure generated by both the 4.5mm and 6.5mm tracheal tubes.

Figure 3-12: Resistance flow relationships of the adult flow sensor with different tracheal tubes attached.



The linear increase in resistance with increase in flow was demonstrated by the addition of a 4.5mm and 6.5mm tracheal tube. The relative resistance of the adult flow sensor (no tube) was comparatively negligible.

Table 3-3: R_{app} and R_{TT} through adult sensor at variable flows

Flow (L/min)	*Flow (L/s)*	*R_{APP} (no tube) $cmH_2O/L/s$*	*R_{TT} (6.5mm) $cmH_2O/L/s$*	*R_{TT} (4.5mm) $cmH_2O/L/s$*
18	0.3	0.04 (0.08)	4.51 (0.12)	13.8 (0.41)
30	0.5	0.16 (0.05)	5.99 (0.14)	21.3 (0.39)
45.6	0.76	0.22 (0.04)	8.14 (0.10)	30.7 (0.72)
60	1.0	0.28 (0.04)	10.2 (0.17)	39.6 (0.41)
73.2	1.22	0.35 (0.05)	12.3 (0.12)	46.6 (0.72)
84.6	1.41	0.38 (0.04)	13.7 (0.28)	55.1 (0.32)

Results are expressed as mean (SD)

The adult flow sensor contributed less than 3% of the total R_{app} for the flow sensor and 6.5mm tracheal tube combined and considerably less for the other tracheal tube combinations. It would therefore represent a negligible proportion of the total R_{rs} in the ventilated child.

3.1.4 Accuracy of resistance calculations

It was not possible to check the resistance calculations of the "CO_2SMO Plus" against the pre-set resistance options of the neonatal lung model, since it was impossible to generate a consistent or accurate flow throughout the breath cycle in any of the ventilators available. However, since the accuracy of both pressure and flow recordings on the "CO_2SMO Plus" have been reasonably established (3.1.1 and 3.1.2), the accuracy of R_{rs} recordings should essentially be dependent on the algorithms for R_{rs} being reasonably executed. From 2.2.2, the algorithm used by "CO_2SMO Plus" to calculate R_{rs} (utilising all raw data points throughout the breath cycle) is expressed by:

Equation 3-1

$$R = \frac{\sum V^2 \sum PF - \sum PV \sum FV}{\sum V^2 \sum F^2 - (\sum VF)^2}$$

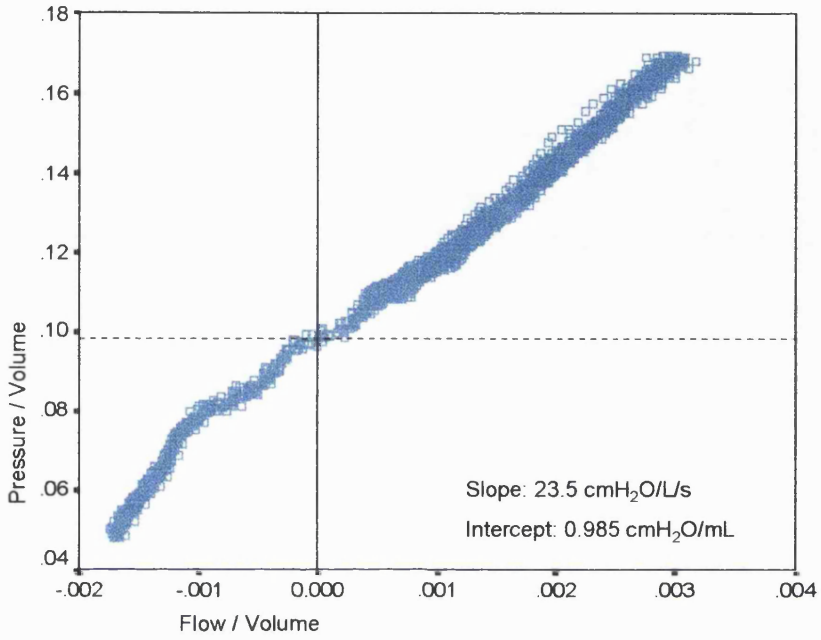
Where R is the resistance of the system, V is the volume, P is the pressure drop at the airway opening (PIP - PEEP) and F is the flow at the model opening. Using raw data from breath cycles obtained from four patients in pilot studies, manual calculations were performed to assess whether R_{rs} values calculated by the "CO_2SMO Plus" could be reproduced. In addition, the same raw data were plotted using a linear function based on the equation of motion, where the slope of the function was R and the intercept was E.

Equation 3-2

$$\frac{P}{V} = \frac{F}{V} \times R + E$$

In all the cases assessed, the value calculated by "CO_2SMO Plus" was comparable to the value obtained from manual calculation as well as the slope of the linear function. For example in one individual (Figure 3-13), the "CO_2SMO Plus" value for R_{rs} was 26.1 $cmH_2O/L/s$ while the manual recalculation yielded a value of 24.3 $cmH_2O/L/s$ and the slope of the linear regression model suggested a value of 23.5 $cmH_2O/L/s$.

Figure 3-13: Linear expression (from the equation of motion) of C_{rs} and R_{rs} from several breaths in one individual



The linear expression of pressure/volume plotted against flow/volume yielded a slope (R_{rs}) of 23.5 $cmH_2O/L/s$ which compared favourably with the calculated value for R_{rs} (26.1 $cmH_2O/L/s$). The y intercept (1/C) suggested a C_{rs} value of 1.02 mL/cmH_2O, which was identical to the calculated value of C_{rs} (1.02 mL/cmH_2O).

3.1.5 Accuracy of compliance calculations

3.1.5.1 Method

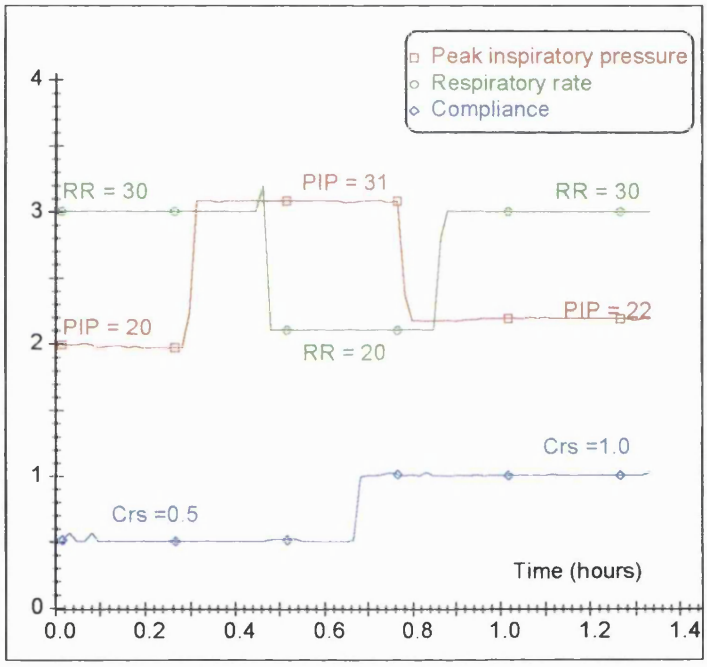
The neonatal sensor was used to assess the accuracy of compliance calculations against the known compliance values of the Manley neonatal lung simulator (SLE). The lung simulator offered compliance settings of 0.5, 1.0 and 3.0 mL/cmH_2O. The neonatal sensor was connected directly between the lung simulator and either a Servo 300 or Bear Cub ventilator. The Servo 300 was used to produce volume controlled (VC) and pressure regulated volume controlled (PRVC) ventilation modes. The Bear Cub was used to produce pressure controlled modes.

The "CO_2SMO Plus" compliance recordings were evaluated against the set compliance of the neonatal lung throughout a range of clinically appropriate peak pressures and respiratory rate settings (Figure 3-14). These assessments were repeated using different ventilation modalities (pressure control, volume control and pressure regulated volume

control). The simulator additionally offered variable resistance of 100, 200 and 400 $cmH_2O/L/s$ and "lung" resistance was varied to assess the impact of these variations on the ability of the "CO_2SMO Plus" to calculate C_{rs} accurately.

The neonatal lung simulator did not have the volume capacity to cope with the higher flow and pressure required to test the paediatric and adult sensors. Compliance calculations were therefore not evaluated in the two larger sensors.

Figure 3-14: Example of C_{rs} measurements with lung model settings of 0.5 and 1.0 mL/cmH_2O during changes of PIP and respiratory rate.

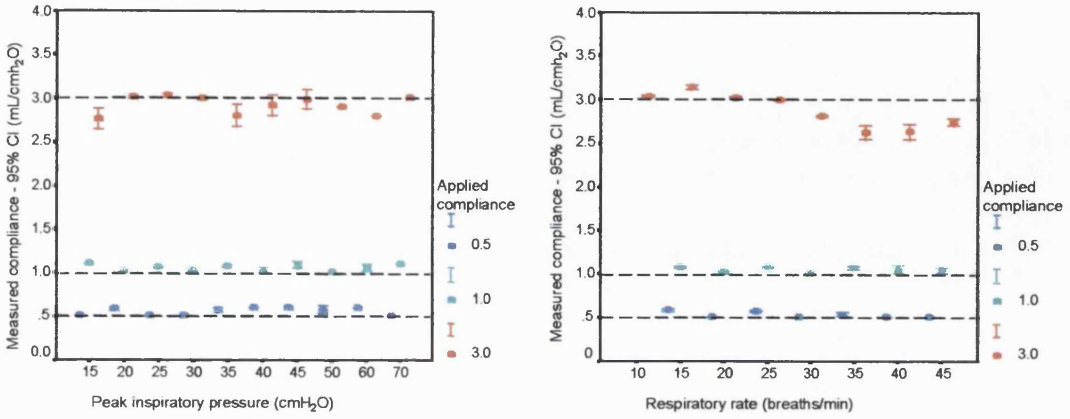


The values of C_{rs} calculated by "CO_2SMO Plus" compared favourably with the set compliance values of the neonatal lung despite changes in respiratory rate and PIP.

3.1.5.2 Results

In all modes of ventilation, volume or pressure was changed to produce a peak inspiratory pressure (PIP) between 15 and 70 cmH_2O and respiratory rate was varied between 15 and 45 breaths/min. C_{rs} recordings by the "CO_2SMO Plus" (using the Least squares method) varied between 0.5 and 0.6 at the lung setting of 0.5 mL/cmH_2O and between 1.0 and 1.1 when the lung was set at 1.0 mL/cmH_2O (Figure 3-15). The disadvantage of the "CO_2SMO Plus" displaying C_{rs} to only one decimal point was that it was not possible to assess whether accuracy was within 10 or 20% error. Accuracy was not influenced by mode of ventilation, respiratory rate, or change in resistance.

Figure 3-15: Influence of PIP and respiratory rate on measured compliance, with lung model settings at 0.5, 1.0 and 3.0 mL/cmH_2O



Calculated values of C_{rs} remained relatively accurate throughout different ranges of PIP and respiratory rate. The "CO_2SMO Plus" had a slight tendency to overestimate the lung-model compliance set at 0.5 and 1.0 mL/cmH_2O, but measurement error remained <8% throughout the range of PIP and RR tested. Note the frequency dependence of C_{rs} calculations when the lung model was set to C_{rs} = 3 mL/cmH_2O.

While most calculated values of C_{rs} remained accurate throughout different ranges of PIP and respiratory rate, when the neonatal lung was set at a compliance of 3.0 mL/cmH_2O, the "CO_2SMO Plus" calculations for C_{rs} displayed frequency dependence with increasing inaccuracy as respiratory rate increased. This was of limited concern however, since neonates in a clinical environment with very compliant lungs would be unlikely to require respiratory frequencies above 35 breaths per minute. C_{rs} was calculated with acceptable measurement errors when ventilation settings were within reasonable clinical range (Table 3-4: respiratory rate < 36 bpm and PIP < 30 cmH_2O). In addition, R_{rs} appeared to influence calculations of C_{rs} when the lung-model was set to a compliance of 3.0 mL/cmH_2O, with calculations becoming more inaccurate with increasing R_{rs}. While the combination of compliant lungs and high respiratory system resistance could potentially introduce errors in measurement, it would rarely be encountered in a clinical setting. Under these circumstances, the underlying assumptions of a single compartment lung model (2.2) would probably not apply and calculations of respiratory mechanics would be unreliable. The combination of moderate to high respiratory rate (20 - 30bpm) and high resistance (400 cmH_2O/L/s) resulted in gross inaccuracy.

Table 3-4: Mean C_{rs} calculations by the "CO_2SMO Plus" compared with set C_{rs} on neonatal lung simulator (variable ventilation settings)

	Neonatal lung model compliance	*Recorded compliance*	*CV (%)*	*% Error*
PC Ventilation	0.5	0.51 (0.03)	5.8	2.0%
	1.0	1.02 (0.04)	3.9	2.0%
	3.0	2.93 (0.14)	4.8	-2.3%
VC Ventilation	0.5	0.51 (0.03)	6.0	2.0%
	1.0	1.06 (0.05)	4.7	6.0%
	3.0	2.97 (0.21)	7.0	-1.2%
PRVC	0.5	0.54 (0.05)	9.2	8.0%
Ventilation	1.0	1.03 (0.02)	1.9	3.0%
	3.0	2.98 (0.15)	5.0	-0.6%

The 2-point compliance (C_{2pt}), calculated by "CO_2SMO Plus" using only points of zero flow during the breath cycle (Mead-Whittenberger technique) was consistently less accurate than the C_{dyn} calculations. The C_{dyn} parameter, using all data points throughout the breath cycle was therefore used preferentially as an outcome parameter in this study.

3.1.6 Accuracy of CO_2 recordings

3.1.6.1 Method

Two neonatal, paediatric and adult flow sensors were connected in turn to a circuit with two known CO_2 gas concentrations, 5% and 5.6% (H.P. CAL 1 Gases, expire 08/2001). In each case connection was interrupted with and without re-calibration to assess whether concentration of gas returned to zero immediately upon disconnection and whether re-calibration was essential after each disconnection.

3.1.6.2 Results

Results are demonstrated in Table 3-5. Although there was a slight tendency to under-estimate gas concentration, measurement errors were always less than 5% and variability was extremely small for all sensors. Upon disconnection and reconnection, CO_2 measurements returned rapidly to zero and reached accurate mean values within three

seconds. There were negligible between-sensor differences in accuracy and baseline values were no different to those obtained after reconnection with or without re-calibration. The "CO_2SMO Plus" is designed to alert the user when calibration is necessary. These values were considered to be very accurate for the purposes of the study.

Table 3-5: Accuracy of CO_2 measurements

Sensor	*Applied gas (%)*	*Measured gas (%)*	*% Error*	*CV (%)*
Neonatal	5.0	4.91 (0.08)	-2.0%	1.67
	5.6	5.60 (0.06)	0.0 %	1.05
Paediatric	5.0	4.77 (0.05)	-4.6%	0.95
	5.6	5.57 (0.07)	-0.5%	1.00
Adult	5.0	4.82 (0.05)	-3.5%	1.01
	5.6	5.53 (0.07)	-1.3%	1.09

3.1.7 Deadspace measurements

No specific studies were undertaken to validate deadspace measurements by the "CO_2SMO Plus", since considerable work had been done by contemporary studies to assess accuracy of these measurements and it was felt that they were sufficiently robust to be relied upon for the purposes of this study (Wenzel et al. (b) 1999; Wenzel et al. (c) 1999).

The "CO_2SMO Plus" software calculated V_D/V_T from the modified Bohr equation using $PeCO_2$ from $SBCO_2$ analysis and the $PaCO_2$ obtained from the arterial blood gas. The $PaCO_2$ values were entered into the software program whereupon the deadspace calculation was automatic. Lum et al (1998) compared the accuracy of $V_{D_{phys}}$ measurements using either a metabolic monitor or Douglas bag method in intubated paediatric patients. The $V_{D_{phys}}/ V_T$ was calculated for both techniques using the Enghoff modification of the Bohr equation in 16 paired measurements in 12 children. The two methods correlated well ($r^2 = 0.99$; $p < .0001$) and the authors concluded that $V_{D_{phys}}/ V_T$ could be measured reliably and accurately in intubated paediatric patients using a metabolic monitor which offered a convenient and simple alternative to the standard Douglas bag method (Lum et al. 1998).

Wenzel et al (1999) performed *in-vitro* and *in-vivo* assessments of the Ventrak 1550/Capnogard 1265 (now the "CO_2SMO Plus") to assess the validity of its deadspace measurements in a lung model and in adult rabbits. Three methods of measuring deadspace (automatic computation, interactive carbon dioxide-volume plot analysis and the Bohr equation) were tested by comparing known added deadspace volumes with calculated added deadspace. The added deadspace was slightly underestimated by all methods, but least by the Bohr equation method. The larger the added deadspace, the lower the absolute errors and coefficients of variation (CV). The highest CV occurred for automatic analysis (approximately 11%) compared with < 6% for interactive analysis or the Bohr method. The authors concluded that automatic computation was sufficiently accurate if changes in deadspace >5mL were anticipated but recommended interactive analysis or the Bohr equation for changes in deadspace < 5 ml (Wenzel et al. (b)1999). In a further study by the same group, it was found that automatic computation and interactive carbon dioxide-volume plot analysis were not possible in two thirds of studies carried out on ventilated neonates, especially in preterm neonates, because of disturbed signals. Deadspace measurements were possible in all cases by use of the modified Bohr equation. Of some concern was the fact that transcutaneous PCO_2 rose above baseline by 3.2% after insertion of the sensor (dead space 2.6 mL) in patients > 2500g and by 5.7% in patients < 2500g. $V_{D_{phys}}$ and $V_{D_{phys}}/ V_T$ values obtained were comparable to data obtained from the literature (Wenzel et al. (c)1999). After this study, the neonatal sensor was redesigned to comprise an added deadspace <1mL, which is much less likely to influence PCO_2 values in term infants significantly. The current study involved measurements of respiratory function in full term neonates or older infants and children, in whom this added deadspace was likely to be negligible.

4. Study design and methodology

The project was granted approval by the Institute of Child Health and Great Ormond Street Hospital for Children, NHS Trust Research Ethics Committee and written, informed consent was obtained from parents of infants and children who were recruited into the study.

4.1 Hypotheses and aims of the study

The core methodology of this study involved measurements of respiratory function in ventilated children using a relatively new monitoring device ("CO_2SMO Plus"). An essential part of the study therefore involved validation of the "CO_2SMO Plus" in terms of its accuracy and practical usefulness in the ventilated paediatric population. There were three major hypotheses:

Hypotheses:

1. The "CO_2SMO Plus" offers a useful clinical tool for evaluating the clinical effects of therapeutic interventions.
2. Respiratory physiotherapy in the paediatric intensive care unit improves respiratory function by:
    - Increasing tidal volume (V_T) and compliance (C_{rs})
    - Decreasing resistance (R_{rs}) and physiological deadspace ($V_{D_{phys}}$),
    - Improving gas exchange as defined by improvement in CO_2 parameters ($ETCO_2$, VCO_2 and $PeCO_2$) and arterial blood gases.
3. Respiratory physiotherapy is more effective than nursing suction at removing secretions and thereby improving respiratory function.

Aims:

The aims of the study related broadly to the two principal objectives, namely to evaluate the validity of the "CO_2SMO Plus" respiratory monitor and to investigate the effects of physiotherapy treatments on respiratory function.

The principal aims of the study were:

- **To evaluate the validity and clinical usefulness of the "CO_2SMO Plus" in the intensive care unit**. To accomplish this, *in-vitro* validation procedures were planned, as well as pilot studies and *in-vivo* tests to ensure that the "CO_2SMO Plus"

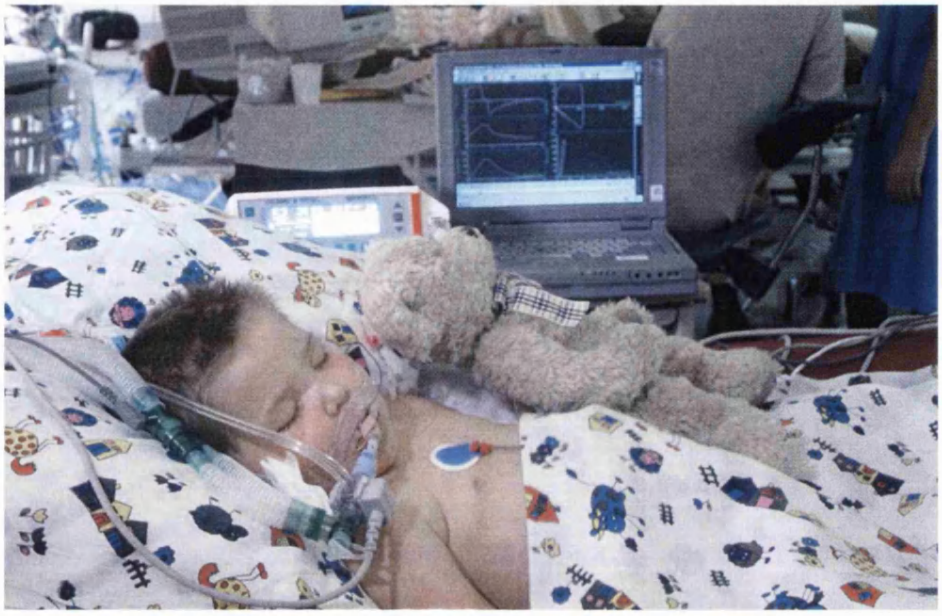
was an accurate and useful tool for measuring respiratory function in ventilated children. Details of these tests and their results are found in sections 3 and 5.

- **To evaluate the efficacy of respiratory physiotherapy techniques in the paediatric intensive care unit**. To accomplish this, neonates, infants and children with different diagnoses who were receiving physiotherapy treatments were recruited for measurements of respiratory function before and after such treatment. The ultimate aim of the study was to analyse and interpret data obtained appropriately and to disseminate findings and suggest changes in practice if these were indicated.
- **To establish whether respiratory physiotherapy treatments offer a significant advantage over routine airway clearance techniques used by nursing staff in ventilated children**. To accomplish this, effects of physiotherapy treatments as well as effects of nursing suction needed to be independently established so that statistical tests could be performed on the mean differences in individuals in whom data had been collected for both techniques.

4.2 Study design and protocol

The study involved a simple cross-over design in which patients were randomly allocated to receive either physiotherapy treatment or routine airway clearance by nursing staff in the morning and the alternative intervention in the afternoon of the same day. Specific protocol details may be found in the Appendix (10.3). In essence, after recruitment and randomisation, a neonatal, paediatric or adult flow sensor was selected according to the age, body weight and ventilator settings of the patient and the sensor was attached between the tracheal tube and ventilator tubing so that continuous recordings of respiratory function measurements could be made. The sensor was left in situ for the duration of the study (usually most of the day) so that trends in respiratory function could be assessed but the critical data collection periods were at least 15 minutes before and 30 minutes after both physiotherapy and nursing suction treatments. Arterial blood gases were taken immediately before and 25-35 minutes after both nursing suction and chest physiotherapy. No ventilator changes or other clinical or nursing interventions were performed during the data collection periods. In the event that no other clinical interventions were performed after either treatment, longer periods following treatment were analysed.

Figure 4-1: Four year old boy with "CO_2SMO Plus" flow sensor attached between tracheal tube and ventilator tubing.



The "CO_2SMO Plus" monitor and online recording on the portable computer are evident in the background.

At least two hours were permitted between the end of one treatment and the beginning of the next, unless, as on rare occasions, a second treatment was indicated earlier. This period was long enough to assess the duration of clinical effect of each intervention as well as short enough to permit the child to act as his or her own control. Trend data were collected continuously between interventions to allow some indication of major changes in the child's clinical status. Some of the inclusion criteria in the final protocol were adapted from results of pilot studies and *in-vivo* studies (section 5).

4.2.1 Study population and inclusion criteria

Infants and children were recruited into the study if they fulfilled the inclusion criteria and if their parents had consented to participate in the study. Once patients were identified as eligible for participation, parents were given the information sheet (Appendix 10.1) and an explanation of the study and allowed time to consider whether they would consent to participation in the study. Recruitment was difficult if parents arrived late in the day and was always difficult because of the stress experienced by parents of extremely ill infants and children.

- Fully ventilated patients were recruited from the cardiac intensive care unit (CICU) or paediatric intensive care unit (PICU). Patients from the neonatal intensive care unit (NICU) were excluded because of concerns that the flow sensor would substantially increase apparatus deadspace and because physiotherapy interventions are rarely performed on preterm infants in this institution.
- Recruited subjects had been pharmacologically paralysed and sedated with analgesia according to unit protocols using standard doses of vecuronium (2-4 mcg/kg/min), morphine (10-40mcg/kg/hr) and midazolam (1-6 mcg/kg/min). Muscle relaxation and sedation were instituted for clinically indicated reasons and not for the purposes of data collection. In the absence of spontaneous respiratory efforts, valid measurements of C_{rs} and R_{rs} were possible and variations in respiratory rate or V_T due to patient effort rather than treatment effect were removed. In addition, the wide within subject variability of respiratory parameters in spontaneously breathing subjects would make it difficult to distinguish treatment effect from data "noise" (section 5.1.2).
- Subjects were recruited if they were receiving physiotherapy treatments and were likely to continue requiring such interventions. Clinical indications for physiotherapy interventions include changes on chest radiograph, added or decreased breath sounds on auscultation, increasing ventilatory requirements and/or deteriorating blood gases. The physiotherapist managing each patient made the decision about whether treatment was indicated.
- Subjects were recruited if they were likely to continue requiring pharmacological paralysis and full ventilatory support for the duration of the data collection interval (at least 8-10 hours following recruitment).
- Subjects were recruited if there was an arterial line in situ for sampling of arterial blood for analysis.
- Subjects were recruited if there was no audible or clinically obvious tracheal tube leak. Unfortunately, it was not always possible to assess magnitude of leak prior to the commencement of monitoring, since such data were rarely displayed or inaccurately displayed on available ventilatory equipment. If after monitoring had commenced, the magnitude of tracheal tube leak was greater than 20%, efforts were made to reduce the airway leak by repositioning the child and if these were unsuccessful, the registrar or consultant was informed, so that the tracheal tube could be changed. Data were only analysed when the mean tracheal tube leak was less than

20% for the duration of the data collection intervals before and after treatment (section 5.2.1).

Since only paralysed or extremely well sedated patients were recruited from the PICU and CICU populations, the selection of patients was likely to be specific and limited to a relatively narrow range of clinical conditions. The CICU population would almost all be surgical patients, younger than three months, having undergone primary repair of major congenital cardiac defects such as transposition of the great arteries, truncus arteriosus and hypoplastic left ventricle. In addition many of these patients, following major cardiac surgery would have delayed sternal closure. A minority of patients would have been admitted to CICU with meconium aspiration and pulmonary hypertension. In general CICU patients would be paralysed in the early post operative period, to assist in establishing haemodynamic stability, reducing pulmonary oedema, managing pulmonary hypertension or when delayed sternal closure necessitated pharmacological paralysis. Patients would almost without exception be recruited to the study within the second or third day of surgery.

By contrast, pharmacologically paralysed patients in the PICU, would consist of children within all age groups, including some with acute or chronic respiratory failure, some following head injury and some following major elective surgical procedures such as gastric transposition. In these patients, the purpose of pharmacological paralysis would vary according to the diagnosis: at times to reduce mobility (gastric transposition), at times to reduce intra-cranial pressure (head injury), at times to allow optimal delivery of ventilation (respiratory failure).
In general a pharmacologically paralysed paediatric population would be associated with significant severity of illness, haemodynamic, cardiac or respiratory instability and the potential for physiotherapy treatments or suction to be poorly tolerated. However, because of the inability of this patient group to move or clear secretions, they would be particularly vulnerable to respiratory complications associated with ventilation.

The predominant mode of ventilation encountered in the neonatal and younger patient groups in the CICU would be lung protective pressure preset modalities,

while the modalities used in the PICU population were broader, including volume preset and pressure regulated modalities. Choice of ventilation modalities in both units would be dependent upon age, pathology, clinicians preference and sometimes availability of ventilator types. More demographic detail on the patients in the study population are given in 6.1.

4.2.2 Therapeutic interventions

Physiotherapy treatments and nursing suction procedures for ventilated children are not prescriptive or protocol driven at this hospital. Both interventions were therefore flexibly defined to allow comparison of techniques in which clinical judgement and constant modification of procedure were an essential part of the therapy. However treatment details of each nursing and physiotherapy intervention were carefully recorded so that information about the most typically performed physiotherapy and nursing treatments could be analysed.

The interventions were defined as any combination of the following techniques and as many or few cycles considered necessary by the physiotherapist or nurse. Not all elements were required.

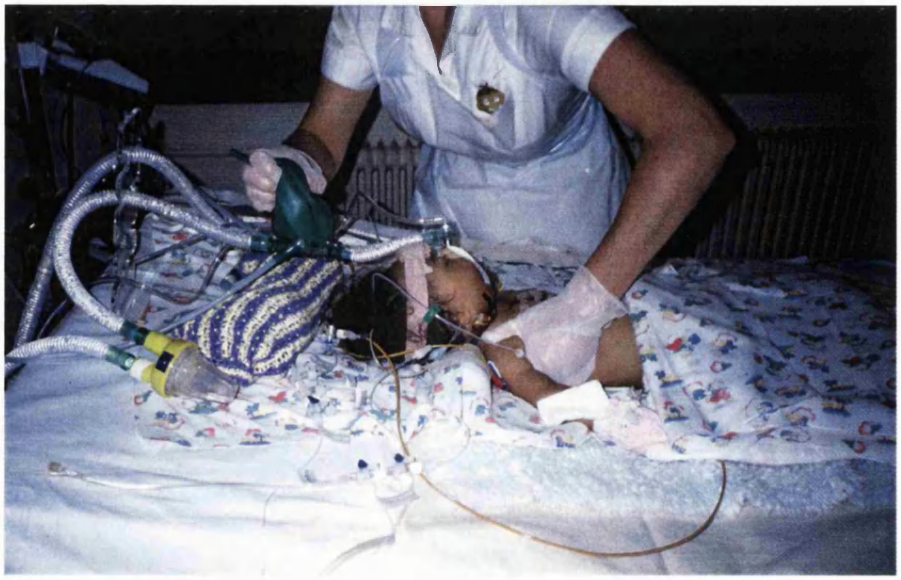
The physiotherapy intervention:

- Saline instillation
- Manual ventilation for hyperinflation or pre-oxygenation
- Chest wall vibration
- Suction
- Postural drainage
- Chest wall compression
- Chest wall percussion

The nursing intervention:

- Saline instillation
- Manual ventilation for hyperinflation or pre-oxygenation
- Suction

Figure 4-2: Physiotherapist performing manual hyperinflation with chest wall vibrations during expiration.



4.2.3 Outcomes

Outcomes of interest included tidal volume (V_T), compliance (C_{rs}), resistance (R_{rs}), end-tidal CO_2 ($ETCO_2$), CO_2 elimination (VCO_2), mixed expired CO_2 ($PeCO_2$), respiratory deadspace volumes ($V_{D_{phys}}$, $V_{D_{alv}}$, $V_{D_{airway}}$ and $V_{D_{phys}}/ V_T$) and arterial blood gases (pH, $PaCO_2$, PaO_2, HCO_3-, base excess and O_2 saturation). Although it was important to assess the behaviour of each parameter independently, respiratory parameters are frequently interrelated: an increase in one often occurs with a simultaneous decrease or increase in another. It was therefore considered important to review changes in parameters relative to each other.

Respiratory rate, PIP, V_{TE} and MV may be partly determined by the ventilator settings and partly determined by patient effort. In the presence of spontaneous ventilatory effort, any or all of these parameters may have been expected to change in response to a physiotherapy treatment as a result of several factors including removal of secretions, increased anxiety, increased metabolism or arousal from sedation. For the purposes of this study however, recruited subjects were all paralysed or heavily sedated so that no efforts at spontaneous respiration were made. Respiratory rate therefore did not vary as a result of physiotherapy treatments and was not influenced by pressure (PC) or volume

controlled (VC) mode of ventilation. However changes in V_{TE} and PIP were determined by both treatment effect and the mode of ventilation.

Patients ventilated with a PC mode maintained constant levels of PIP, MAP and PEEP before and after treatment, while V_{TE} was potentially variable. Changes in C_{rs} or R_{rs} as a result of the physiotherapy treatment would have been expected to result in changes of V_{TE}. An increase in C_{rs} or reduction in R_{rs} would generally be accompanied by an increase in V_{TE} and vice versa. By contrast, patients ventilated with a VC mode maintained constant V_{TE} before and after treatment, while PIP and MAP were potentially variable. In this instance, changes in C_{rs} or R_{rs} after treatment would be expected to result in changes to the measured pressures. An increase in C_{rs} or decrease in R_{rs} would be associated with a drop in PIP, while PIP would increase if C_{rs} decreased or R_{rs} increased. Since mode of ventilation significantly influenced the primary parameter of interest following treatment, analysis of data was performed separately for patients receiving different modes of ventilation.

Important reference data were also collected to ensure that inadvertent changes in ventilation settings had not occurred during data collection. These reference data included respiratory rate, peak inspiratory pressure, positive end expiratory pressure, mean airway pressure, peak expiratory flow, inspired CO_2, inspiratory and expiratory time.

In general, improvement was defined as a significant increase in V_T, C_{rs}, PaO_2 and O_2 saturation, while a change in the opposite direction indicated a deterioration as a result of the intervention. Similarly, decreases in R_{rs}, $ETCO_2$, $PeCO_2$ and respiratory deadspace volumes were considered to indicate improvements in respiratory function while changes in the opposite direction indicated a deterioration as a result of the intervention. Interpretation of changes in isolated parameters can however be misleading and often requires examination of simultaneous changes in related parameters to determine the change in respiratory status accurately. A reduction in VCO_2 for example may be related either to a deterioration in the efficiency of gas exchange (indicated by a simultaneous increase in $PaCO_2$) or to an improvement in clinical status (associated with a simultaneous reduction in $PaCO_2$). Changes in VCO_2 are thus difficult to interpret in

isolation. They require examination in conjunction with simultaneous changes in V_T, $ETCO_2$ and $PaCO_2$.

4.2.4 Measurement tools

The "CO_2SMO Plus" respiratory profile monitor was selected for use in this study because it offered a safe and non-invasive, portable instrument which was accurate, reasonably cost effective and easy to use. In addition on-line recording and display facilities were considered critical for downloading and analysing data. (Broseghini et al. 1988). The advantages of continuous measurement included acquisition of trend data reflecting the way in which respiratory function changed over time in response to interventions such as physiotherapy or nursing suction. Isolated or 'snapshot' measurements may have obscured the dynamic nature of the response of the respiratory system to clinical changes. A small risk of increased unplanned extubation with the added weight of the "CO_2SMO Plus" pneumotachograph in the ventilator circuit has been identified (Numa and Newth, 1995), thus connections were always safely secured to minimise this risk.

The "CO_2SMO Plus" respiratory monitor, like many respiratory measurement systems combined simultaneous measurements of pressure, flow and CO_2 at the tracheal tube opening. From these data, several respiratory parameters were automatically calculated including V_T, R_{rs}, C_{rs} and respiratory deadspace. In addition, flow/volume and pressure/volume loops and single breath CO_2 curves were generated and electronically stored. Arterial blood gases were analysed using portable i-Stat clinical analysers (Hewlett - Packard, USA).

4.3 Data management and statistical methods

The electronic data collection and memory capacity of the "CO_2SMO Plus" meant that immense amounts of data were generated from each patient, both in terms of trended measurements which yielded average values for each minute of recording and waveform data, which yielded real-time breath by breath data at 100Hz. Details of algorithms contained in the software for calculation of respiratory parameters are discussed in chapter 2.0. The memory capacity of the "CO_2SMO Plus" monitor was limited, but a

computer connected to the "CO_2SMO Plus" during recording could provide continuous data recording and storage limited only by the memory capacity of the computer.

4.3.1 Data management

Data electronically recorded by the "CO_2SMO Plus" were exported to Microsoft Excel software. From the Excel program, data were exported to a statistical software program for analysis (SPSS). Once in SPSS, additional respiratory parameters not calculated or displayed by the "CO_2SMO Plus" such as body weight corrected C_{rs}, V_T, VCO_2 and tracheal tube leak were calculated from raw data. Then data collection intervals were identified and separated from the entire set so that mean values and standard deviations could be aggregated for each respiratory parameter, for the 15 minute period before and after both physiotherapy and nursing suction. Mean aggregated values for 30, 45, 60, 75 and 90 minute intervals following treatments were also calculated. These data were entered on a spreadsheet in SPSS, which incorporated data from all patients, as well as demographic information and information about diagnosis, ventilation modality, tracheal tube size and leak, details of the treatment intervention and randomisation. Similarly, arterial blood gas data as well as parameters computed from them were entered into the main spreadsheet. Demographic data were organised into categories to allow analysis according to factors such as age group, diagnosis, ventilation modality or treatment.

4.3.2 Statistical methods

The scarcity of consistent, good quality published data involving respiratory function measurements in fully ventilated paediatric patients meant that prospective power calculations were difficult to perform and it was not possible to anticipate in advance how many patients would be adequate to demonstrate significant changes in particular respiratory parameters (Healy, 1992; Florey, 1993). Knowing that some data might not be technically satisfactory, it was decided to recruit 100 patients so that some analysis of subgroups could be performed. Retrospective power calculations were performed to assess the power of the study sample to detect significant changes in respiratory parameters and these are discussed in 7.4.8.

Various statistical methodologies were used for analysis of data in the pilot, *in-vivo*, and main studies. Bland and Altman analysis was used to assess accuracy of volume and

pressure recordings of the neonatal, paediatric and adult "CO_2SMO Plus" flow sensors with and without tracheal tubes of different sizes in situ. During validation and *in-vivo* studies, the Bland and Altman approach was frequently used to assess the degree of error in the "CO_2SMO Plus" measurements or to see whether these measurements were interchangeable with validated measurement systems (Hans-Rudolph calibrated syringes or validated pressure manometers). The Bland and Altman method recommends plotting the difference between the techniques against the average of the standard and new measurement. This approach provides detailed information not only about the relationship between two parameters, but the magnitude of the absolute difference between them, in terms of a mean difference and the 95% confidence limits of that difference. This enables an estimation of the maximum error that is likely to occur if one method is substituted for another. The width of the confidence intervals depends both on the variability of the relationship between the two techniques and the number of observations. This method is likely to be less misleading than the use of simple regression analysis, which has been frequently used in the past and which may show a strong correlation between two methods, even though one is giving readings that are systematically much greater or smaller than the other. Similarly it avoids the pitfalls of making 'type 2 errors', wherein two methods are stated to be similar because 'there was no statistically significant difference between them', simply because too few subjects were measured for the study to have sufficient power to detect any differences that were present (Bland and Altman, 1986; Bland and Altman, 1995; Bland and Altman, 1999).

Other methods of expressing validation and *in-vivo* results were descriptive, tabulated or graphical depending on which method was considered to summarise the data most efficiently. Demographic data in the main study section were expressed in bar charts and changes due to physiotherapy and nursing suction were examined by standardised paired sample t-tests. Patients with mean tracheal tube leaks larger than 20% during the data collection interval were excluded from analysis and results were confirmed using a general linear model analysis (SPSS) to assess any residual effects of tracheal tube leak in patients with tracheal tube leaks less than 20%. For parameters with large between subject variability, such as R_{rs}, $V_{D_{alv}}$ and $PeCO_2$, results were confirmed with non-parametric Wilcoxon tests.

Finally, in addition to evaluating group changes in parameters following treatment, normal within-subject variability (in the absence of any interventions) was calculated for each measured parameter and the relative percentage changes following treatment were displayed by histogram to illustrate percentage changes in individuals (section 6.6). Changes were compared to normal variability for each parameter. This was to assess the likelihood of changes being clinically significant.

Data from all subjects were pooled in the first instance, and then population sub-groups (according to ventilation mode, age and diagnosis, etc.) were examined separately to determine any differences. The mean changes following physiotherapy were compared to the mean differences after nursing suction in the same individuals, so that differences in techniques, if any, could be identified. ANOVA calculations were used to determine what, if any, characteristics those patients who responded favourably to physiotherapy or nursing suction had in common. Details of analysis are described in appropriate sections.

5. Pilot and *in-vivo* validation studies

5.1 Pilot Study

5.1.1 Introduction

Initial measurements on the intensive care unit exposed areas of concern about the design of the study that required further investigation with a view to revising the initial protocol. The specific areas of concern were that:

1. In the absence of oesophageal manometry, respiratory mechanics could not be measured during spontaneous breathing, and patterns of breathing may be too variable to interpret changes in other parameters.
2. A 15 minute period of recording may be insufficient to represent accurately the baseline status of the child.
3. Variations in the magnitude of tracheal tube leak may adversely affect quality of data obtained.
4. The absence of normative data with regard to physiotherapy and ventilated children made it difficult to determine what changes would constitute clinical significance.

Investigations were therefore undertaken to assess the impact of these factors and are described briefly below:

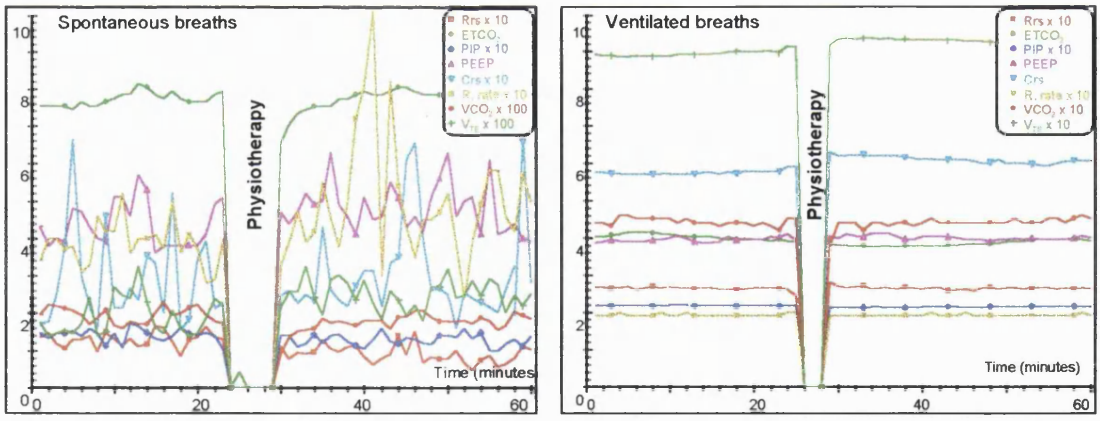
5.1.2 Levels of ventilatory support

Fifteen infants were recruited to the study and had respiratory function measurements before and after physiotherapy and nursing suction. The initial protocol did not exclude patients who were breathing spontaneously or combining spontaneous breaths with mechanically supported breaths. However, it became clear from early studies that:

1. Respiratory function measurements in children making spontaneous efforts had wide within-subject variability which made it very difficult to tease out treatment effect from broad ranges of "noisy" data (Figure 5-1). Variability was minimal in paralysed patients, allowing treatment effect to be more easily identified. In addition, complex interactions between respiratory rate, volumes and pressure in the spontaneously breathing individual would create difficulty in identifying sensitive outcomes.

2. Measurements of respiratory mechanics (R_{rs} and C_{rs}) were not valid in patients making spontaneous respiratory efforts. These children would have required additional oesophageal manometry to differentiate between chest wall and lung mechanics (Sly et al. 1996). Such differentiation was not possible with the "CO_2SMO Plus" alone. Although oesophageal monitoring would have been useful during this study, the complexity of its use was unlikely to recommend it as a pragmatic clinical tool for routine physiotherapy treatments. Since C_{rs} and R_{rs} were considered important outcomes, only fully ventilated, paralysed or heavily sedated infants and children were recruited into the study after completion of the pilot study. A further reason for limiting measurements to paralysed patients was that differences in alveolar ventilation during spontaneous ventilation would lead to non-equilibrium between $PeCO_2$ and $PaCO_2$, and values of $V_{D_{phys}}$ and $V_{D_{alv}}$ would be variable (Taskar et al. 1995).

Figure 5-1: Examples of trended data before and after treatment in a spontaneously breathing and a mechanically ventilated child.



The wide within-subject variability evident in the patient on the left who is breathing spontaneously between ventilator breaths, would make it difficult to distinguish changes as a result of therapy. By contrast, subtle changes in V_{TE} and C_{rs} after physiotherapy in the patient on the right are clearly visible.

5.1.3 Validation of measurement interval:

The choice of measurement interval involved satisfying both the requirement that it was long enough to be representative of the patient's true clinical status while short enough to be clinically realistic amongst the multiple interventions performed on patients in intensive care. The intensive care environment is incompatible with a study design which

incorporates long periods of minimal handling before and after the intervention of interest. The minimum measurement period was therefore chosen to be 15 minutes.

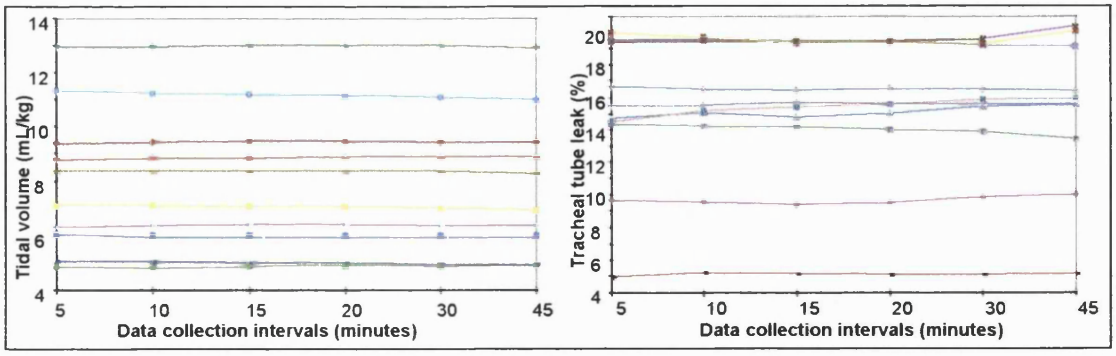
5.1.3.1 Method

In order to assess whether the 15 minute minimal data collection interval would yield results comparable with data collected over a longer period, respiratory parameters were compared over 6 data collection intervals. During periods in which minimal or no clinical interventions were performed, data were collected in 10 paralysed and fully ventilated patients for 45 minutes. Mean values at 5, 10, 15, 20 and 30 minutes were compared to the mean at 45 minutes using the Bland and Altman method of comparison (Bland and Altman, 1999).

5.1.3.2 Results

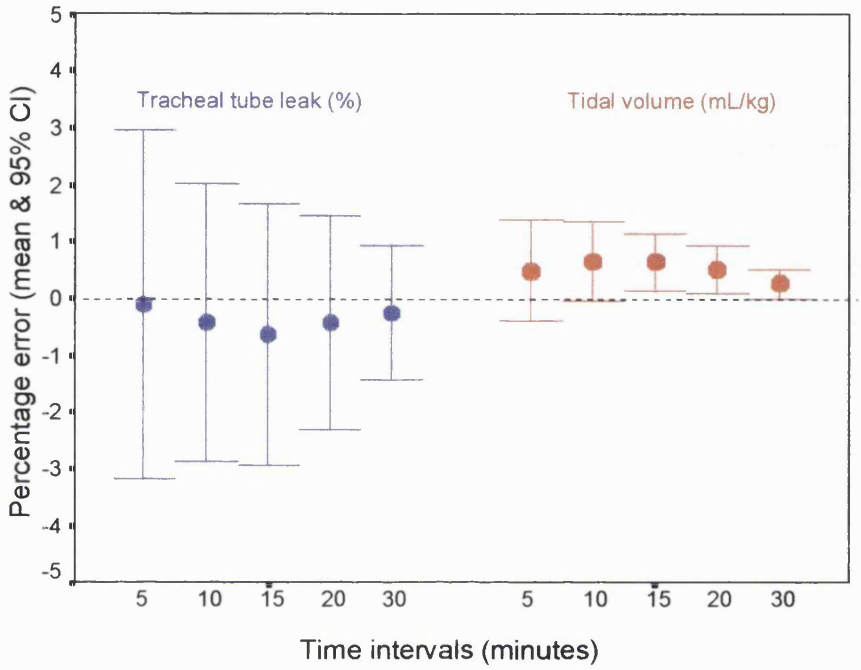
Trended data for all 10 individuals showed very little variation over different measurement intervals. There was considerable inter-subject variability with respect to delivered V_T and tracheal tube leak (Figure 5-2), but for both parameters, percentage difference between the 5, 10, 15, 20 and 30 minute means and the 45 minute "gold standard" was trivial (Figure 5-3).

Figure 5-2: Variability of V_{TE} /kg and tracheal tube leak in 10 individuals during quiet clinical periods



The mean values for tidal volume and magnitude of tracheal tube leak did not change substantially in any individuals (indicated by different colours), whether the measurement period was 5 or 45 minutes. Thus it was felt that in a population of paralysed fully ventilated children, a relatively short baseline measurement interval would be adequate.

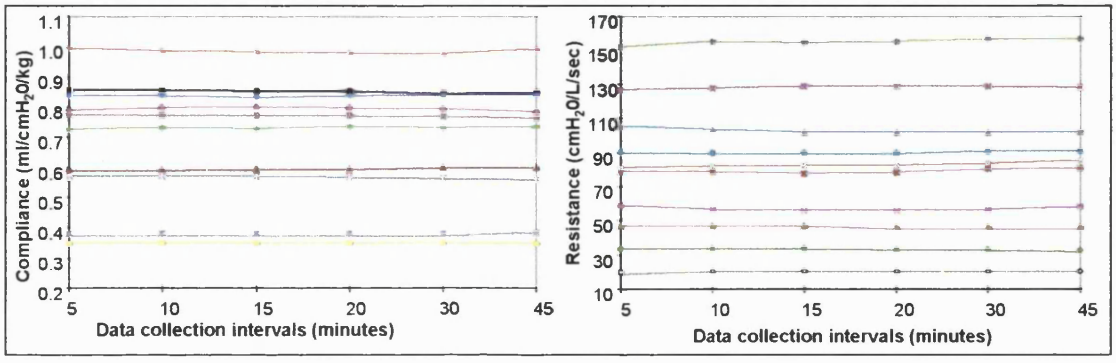
Figure 5-3: Comparison of mean values for different measurement intervals against 45 minute mean.



Mean values of tracheal tube leak and tidal volume percentage error were very similar regardless of measurement interval, but deviation about the mean was reduced as the measurement interval increased. Variability of V_T data was considerably less than that of tracheal tube leak. However, even the 5 minute measurement interval had extremely small confidence intervals, with the 95% limits of agreement less than 10%.

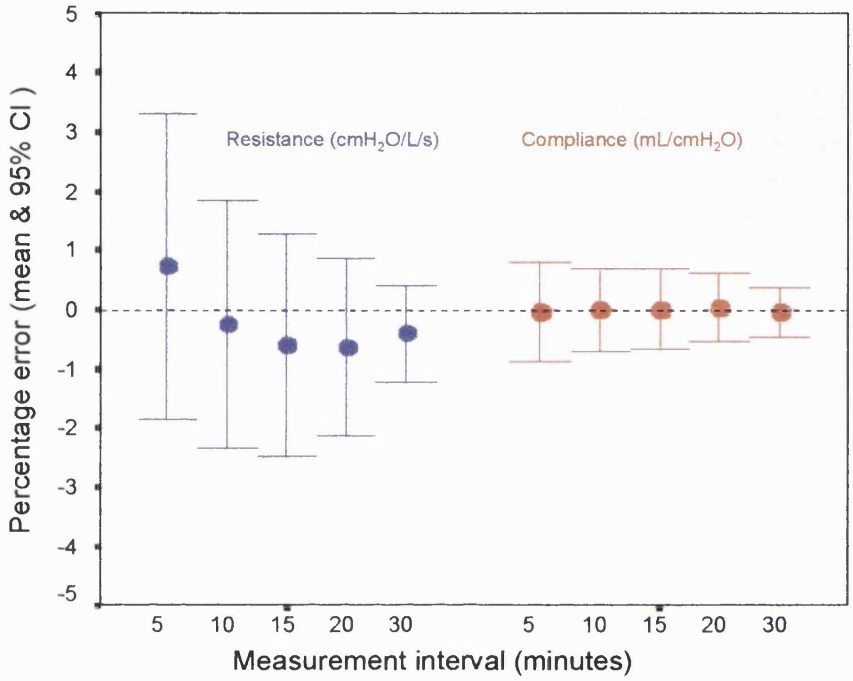
There was a tendency for tracheal tube leak to be underestimated and V_T to be overestimated by negligible amounts during data collection intervals less than 45 minutes. The mean difference never exceeded 1% for either parameter at any measurement interval.

Figure 5-4: Variability of C_{rs} and R_{rs} during quiet clinical periods



Data trends for C_{rs} and R_{rs} similarly showed little variation over different measurement intervals, despite considerable inter-subject variability in calculated values (Figure 5-4).

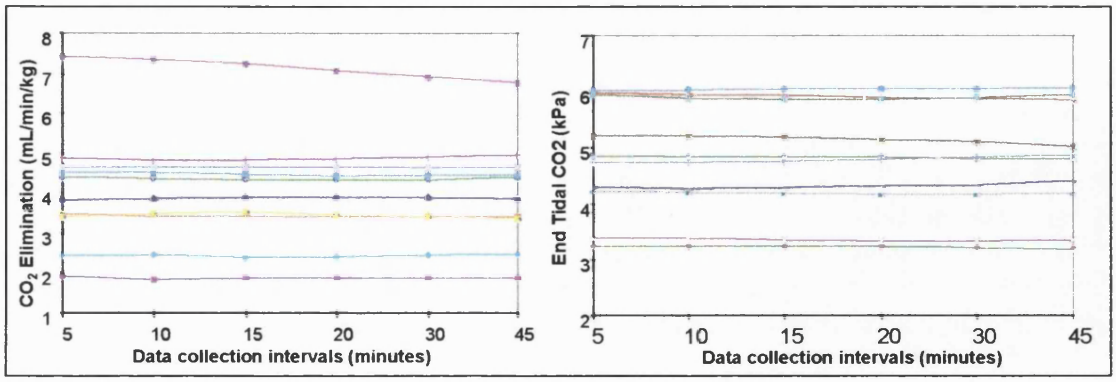
Figure 5-5: R_{rs} and C_{rs} data for different time intervals compared with a 45 minute interval



Mean values of C_{rs} and R_{rs} percentage error approached zero regardless of measurement interval. Deviation about the mean was reduced as the measurement interval increased, but 95% CI for percentage error remained very small, even for the 5 minute measurement interval. Variability of C_{rs} data was considerably less than that of R_{rs}.

From Figure 5-5, the mean percentage difference between the 5, 10, 15, 20 and 30 minute means for C_{rs} and R_{rs} and the 45 minute mean was minimal. Once again deviation about the mean was reduced as the measurement interval increased and as expected, variability of C_{rs} was less than that of R_{rs}. Confidence intervals were small and the widest 95% limits of agreement were <10% for R_{rs} and <5% for C_{rs}, for the 5 minute data collection interval. The mean difference never exceeded 1% for R_{rs} or 0.25% for C_{rs}.

Figure 5-6: Variability of VCO_2 and $ETCO_2$ during quiet clinical periods



The mean values for VCO_2 and $ETCO_2$ did not change substantially in any individuals (indicated by different colours), whether the measurement period was 5 or 45 minutes. On the left, the individual with a relatively high baseline VCO_2 (7.5 mL/min/kg) displays some regression to the mean.

Data trends for CO_2 parameters showed little variation over different measurement intervals, although one individual with an unusually high VCO_2 demonstrated a slowly normalising trend over the 45 minute period (Figure 5-6).

Figure 5-7: Variability of CO_2 parameters, comparing different data collection intervals to a 45 minute interval

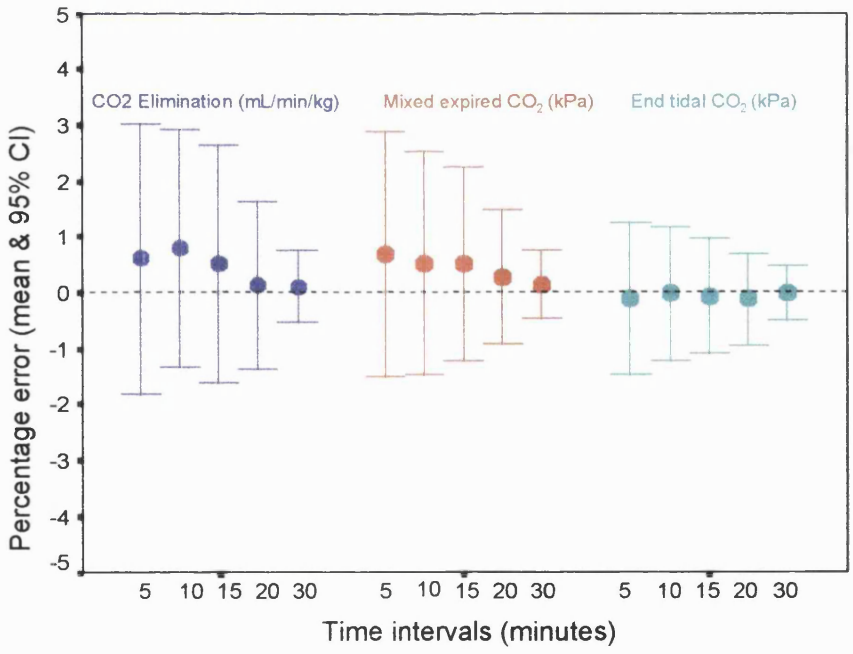


Figure 5-7 demonstrates minimal difference in CO_2 values between the 5, 10, 15, 20 and 30 minute means and the 45 minute mean. As with the other respiratory parameters, deviation about the mean reduced as the measurement interval increased. $ETCO_2$ appeared to have the lowest variability of the CO_2 parameters, although even the widest 95% limits of agreement for the other two did not exceed 8%. There was a (minimal) tendency for VCO_2 and $PeCO_2$ to be overestimated during data collection intervals <45 minutes, although the mean difference never exceeded 1% for VCO_2 and $PeCO_2$ or 0.25% for $ETCO_2$.

The outstanding feature of these recordings was the stability of various respiratory parameters in paralysed patients during quiet clinical periods. The study protocol required at least 15 minutes of baseline measurement and 15 minutes after each treatment. This investigation provided confidence that the data obtained in 15 minutes would be as useful as data obtained during longer periods.

While these data suggested that measurement intervals as short as 5 minutes were sufficient to obtain baseline data in a paralysed patient, there were concerns that even 45 minutes could potentially be insufficient to demonstrate slowly changing parameters as a result of therapy. It was therefore decided that 15 minutes would represent a reasonable compromise as a baseline and post treatment interval. It also represented a measurement interval which most medical or nursing staff would be willing to accommodate in terms of willingness to delay non-urgent interventions (nappy changes, chest radiograph, position change). Efforts were made to ensure at least 2 measurement intervals (30 minutes) were obtained in all patients after treatment, and longer periods in as many patients as possible.

5.2 In-vivo studies

The following investigations were undertaken concurrently with the primary study, but analysed in advance of the primary study data since it was anticipated that the results would influence:

1. which subjects would finally be included in analysis
2. interpretation of results in terms of clinically significant changes.

5.2.1 Tracheal tube leak

Laboratory and animal studies have identified the potential for tracheal tube leak to confound a number of respiratory parameters, including metabolic gas exchange and functional residual capacity (Fox et al. 1979; Knauth and Baumgart, 1990). Patients with a tracheal tube leak have been shown to need higher FiO_2, MAP and respiratory frequency than those without such a leak (Krauel, 1993). Tracheal tube leak has also been found to reduce the mean tracheal pressure with respect to the mean airway pressure by 15-21% in rabbits (Perez et al. 1985). In the presence of lung disease and reduced compliance, gas shunting through the leak pathway is likely to increase, which may further compromise ventilatory support. In diseased lungs, even small airway leaks lead to large reductions in lung recruitment at higher PEEP values, and errors in measuring resistance and compliance have been found to be relatively larger than in healthy lungs for all magnitudes of leak (Pyon et al. 1999).

Several lung model or animal model studies have established that compliance and resistance measurements are overestimated and unreliable in the presence of leak (Kuo et al. 1996; Kondo et al. 1997; Pyon et al. 1999). While these are valuable *in-vitro* results, caution should be exercised when extrapolating these findings to the clinical setting. While errors have been shown to be proportionate to the size of the leak, they also depend on the method used to calculate respiratory mechanics (Kuo et al. 1996). The most commonly used techniques include Mead and Whittenberger's method, multiple linear regression analysis or the least squares method (Sly et al. 1996). Uncuffed tracheal tubes are commonly used to ventilate infants and children because of concerns about subglottic damage. It is quite difficult for clinicians to select a tracheal tube which seals snugly through the cricoid ring. There is therefore often a small leak around which some of the delivered ventilation is lost. Unfortunately there is relatively little information with regard to the effects of leak in the clinical environment or how much leak may be tolerable in ventilated children if reliable measures of respiratory function are to be made.

If the size of the leak changed during the data collection period, improvement or deterioration might erroneously be attributed to treatment effect. It was important therefore, as a subsidiary aim of this study, to assess *in vivo* the influence of tracheal

tube leak on V_T, C_{rs} and R_{rs} in ventilated children and infants. In addition the magnitude and within-subject variability of tracheal tube leak was assessed in order to establish when measurement of V_T, C_{rs} and R_{rs} could be performed reliably in this population.

5.2.1.1 Methods

In 75 of the patients recruited for the primary study, monitoring was continued for at least 5 consecutive hours, during which time nursing and medical procedures such as physiotherapy, postural changes and tracheal suction were performed as usual. These long periods of continuous measurement provided the opportunity to investigate the occurrence, magnitude and variability of tracheal tube leaks during a normal period of intensive care, as well as their consequences for the ventilated child.

Expired tidal volume was integrated from expiratory flow, while compliance and resistance were automatically computed by the "CO_2SMO Plus" throughout the breath cycle using the least squares regression method (Sly et al. 1996). Inspiratory and expiratory resistance were calculated using data from the inspiratory and expiratory portion of the respiratory cycle respectively, whereas data throughout the whole breath were used to calculate compliance (section 2.2).

Inspired and expired tidal volumes, compliance, and resistance were recorded and saved as average values for each minute of recording. Tracheal tube leak was calculated as the difference between inspired and expired tidal volume using the equation:

Equation 5-1

$$\% \text{ leak} = \frac{(V_{TI} - V_{TE})}{V_{TI}} \times 100$$

Changes in tidal volume, resistance and compliance were related to simultaneous changes in leak during the monitoring period.

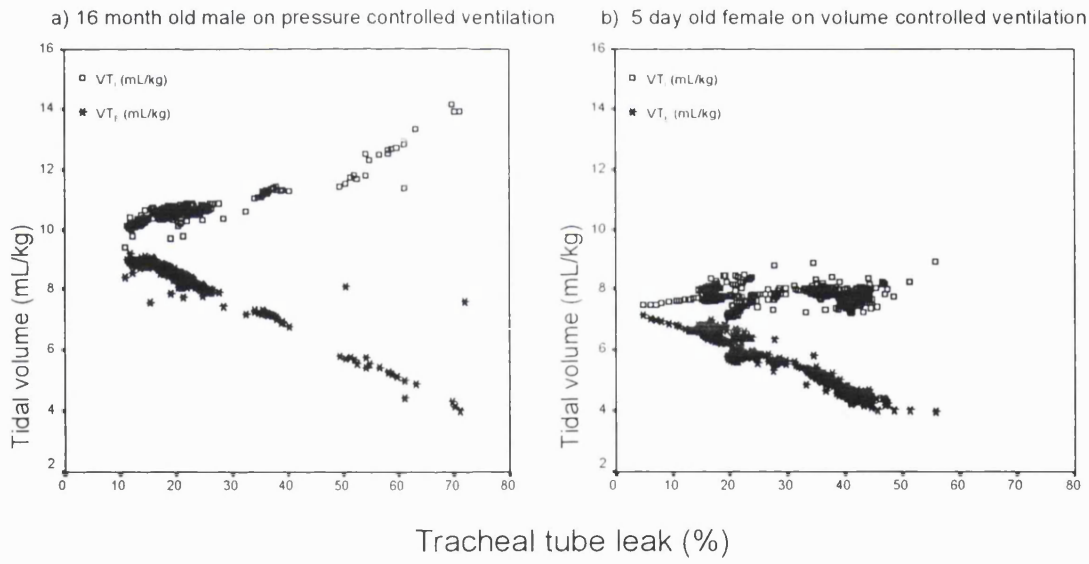
5.2.1.2 Results

Of the 75 paralysed ventilated children studied, 61 had pressure controlled ventilation: median age 0.25 years (0.02 to 12.8 years) and weight 4.3 kg (2 to 87 kg) and 14 had volume controlled ventilation: median age 4 years (0.02 to 10.5 years) and weight 15.8

kg (3 to 30 kg). 4 children in each group had a cuffed tracheal tube: median age 8 years (4 - 16 yrs) weight 22 kg (13.9 - 87 kg). Ten children (13%) had a mean tracheal tube leak greater than 20% (21.9 - 65.1%), median age 0.12 years (0.02 - 1.3 yrs) and weight 2.95 kg (2.6 - 9.8 kg). In the latter group, there were particularly wide within and between-subject fluctuations with respect to the magnitude of leak, V_{TE}, C_{rs} and R_{rs} during the monitoring period.

Figure 5-8 summarises data recorded over several hours in two infants in whom ventilatory settings remained constant during the monitoring period. The relationship between both inspired and expired tidal volume and changes in percentage of leak are displayed.

Figure 5-8: The relationship between V_T and change in tracheal tube leak



The relationship between inspired and expired tidal volume and percentage leak in a) an infant on pressure pre-set ventilation (Servo 300) and b) an infant on volume pre-set ventilation (Servo 300). Tracheal tube leak was calculated from the difference between inspiratory (V_{TI}) and expiratory (V_{TE}) tidal volume. Each data point represents the mean value from one minute of recording

In the first example from a 16 month old male infant on pressure controlled ventilation (Figure 5-8a) the leak varied between 10% and 70% over a six hour period and was accompanied by a 30% increase in inspired tidal volume and a 60% reduction in expired volume. By contrast, but as expected, during volume controlled ventilation (Figure 5-8b) inspired volume remained relatively constant in a 5 day old (2.88 kg) infant over 7

hours of monitoring. This was however, accompanied by a marked reduction in expired volume as the leak increased, with expired tidal volume halving when leak was maximal. In this infant there was a strong negative correlation ($r^2 = 0.93$) between V_{TE} and leak (Figure 5-9). There was also a strong positive correlation between leak and both calculated compliance ($r^2 = 0.68$) and calculated resistance ($r^2 = 0.93$) (Figure 5-10).

Figure 5-9: The relationship between tracheal tube leak and V_{TE}

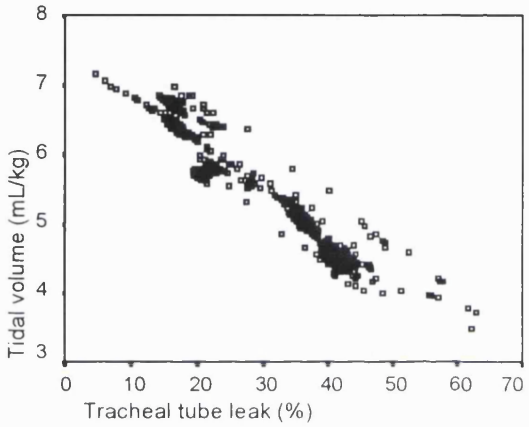


Figure 5-10 The relationship between tracheal tube leak and Crs and Rrs

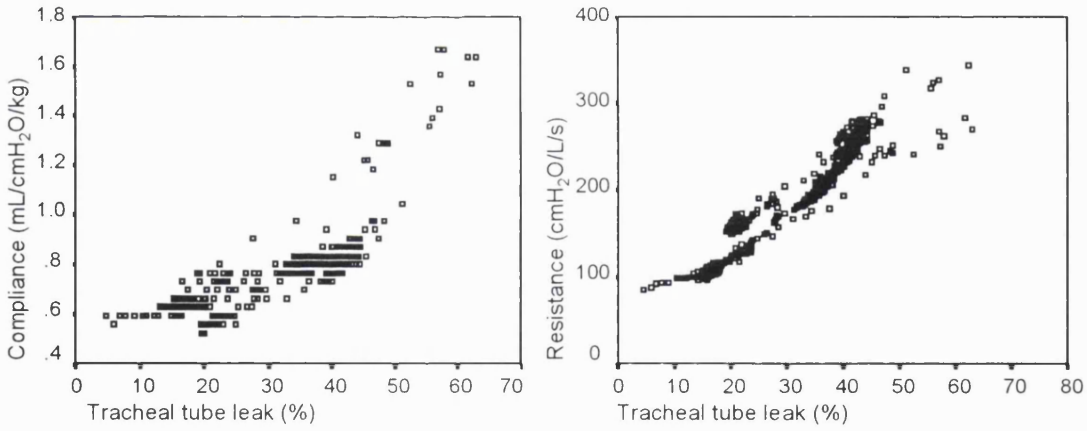


Figure 2: The relationship between tracheal tube leak and V_{TE}, C_{rs} and R_{rs} in a 5 day old infant. Each data point represents the mean value from one minute of recording.

In the presence of a large leak the compliance and resistance values exceeded the physiological limits that would normally be observed in sick ventilated neonates i.e. <1 $mL.cmH_2O^{-1}.kg^{-1}$ and <150 $cmH_2O.L^{-1}.s$ (<10.2 $mL.kPa^{-1}.kg^{-1}$ and <15.3 $kPa.L^{-1}.s$) (Davis et al. 1988; Edberg et al. 1990; Sly et al. 1996; Stenson et al. 1998).

The influence of the large tracheal tube leak on the shape of flow volume and pressure volume curves is illustrated in Figure 5-11 which shows data from a 7 week old (2.6 kg)

baby who was on pressure controlled ventilation, both before and after (Figure 5-12) the tracheal tube was changed from a size 3 to a 4mm tracheal tube.

Figure 5-11: Flow-volume and pressur-volume loops before tracheal tube change in a 7 week old infant.

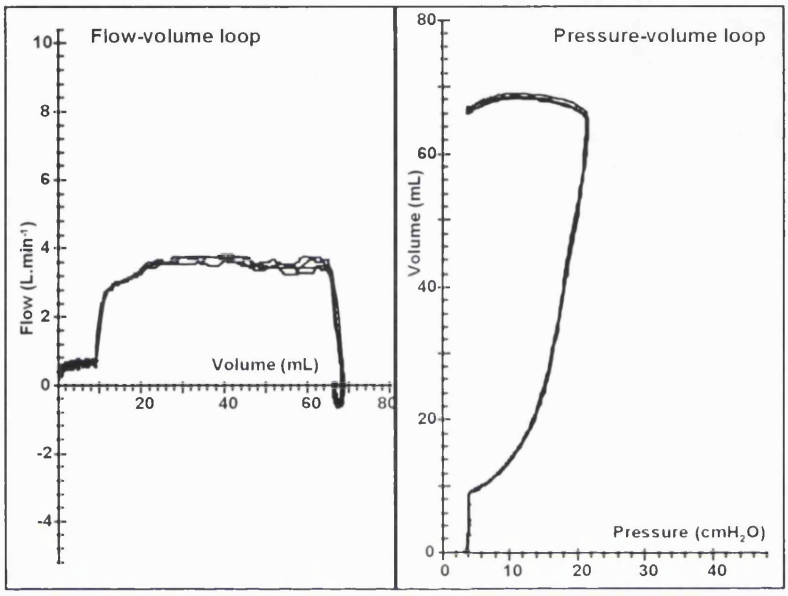
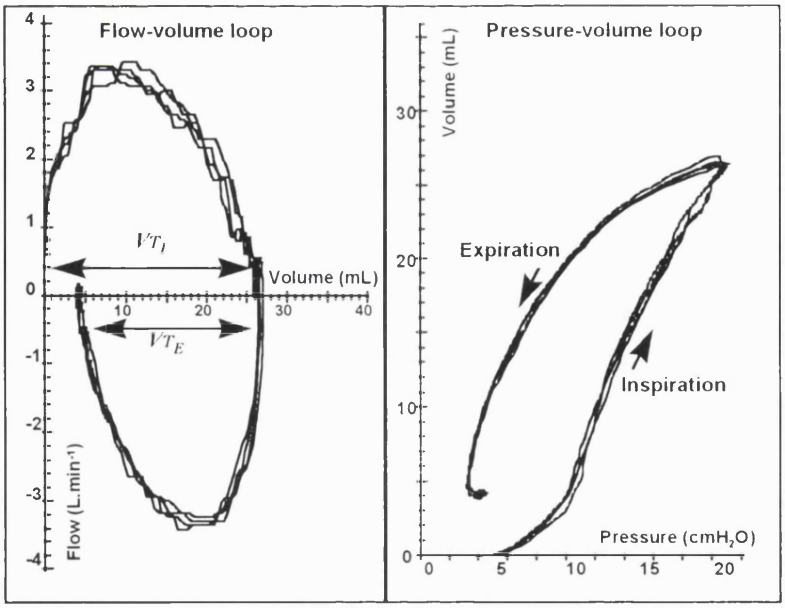


Figure 5-12: Flow-volume and pressure-volume loops after tracheal tube change in a 7 week old infant.



Data were collected for 7 hours prior to and 5 hours after tube change and the V_{TE}, C_{rs} and R_{rs} values relating to the tracheal tube change are displayed in Figure 5-13 and 5-14. Clinical status was stable and ventilator settings not altered during this period suggesting

that the observed changes in tidal volume, compliance and resistance were attributable to the change of tracheal tube.

Figure 5-13: Influence of tracheal tube change on V_{TE}, in a 7 week old infant

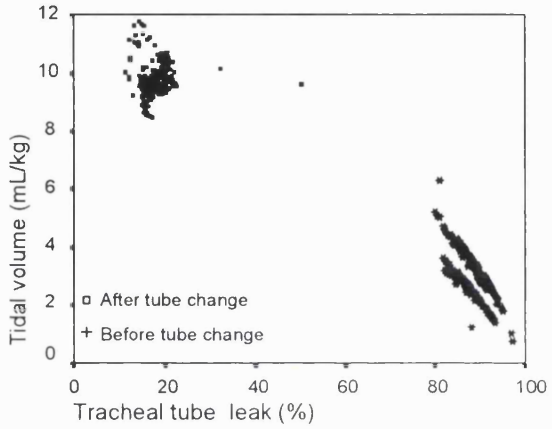
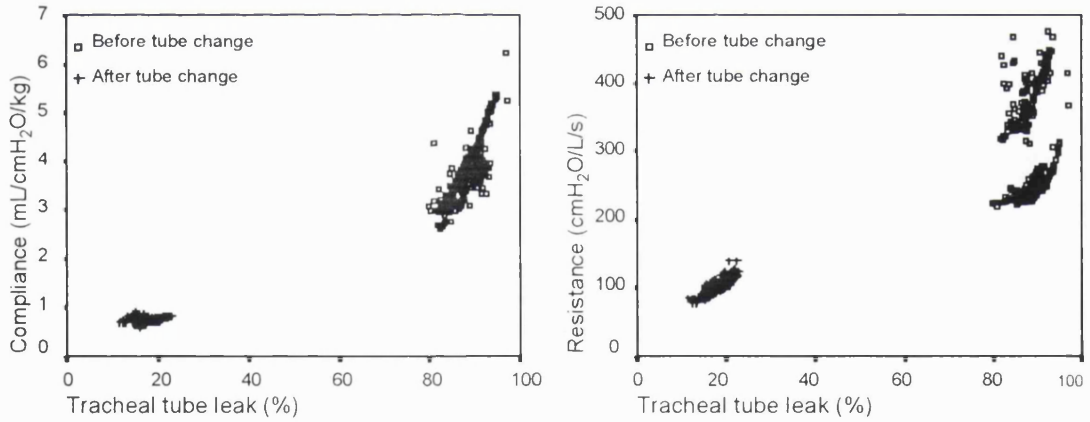


Figure 5-14: Influence of tracheal tube change on Crs and Rrs in a 7 week old infant

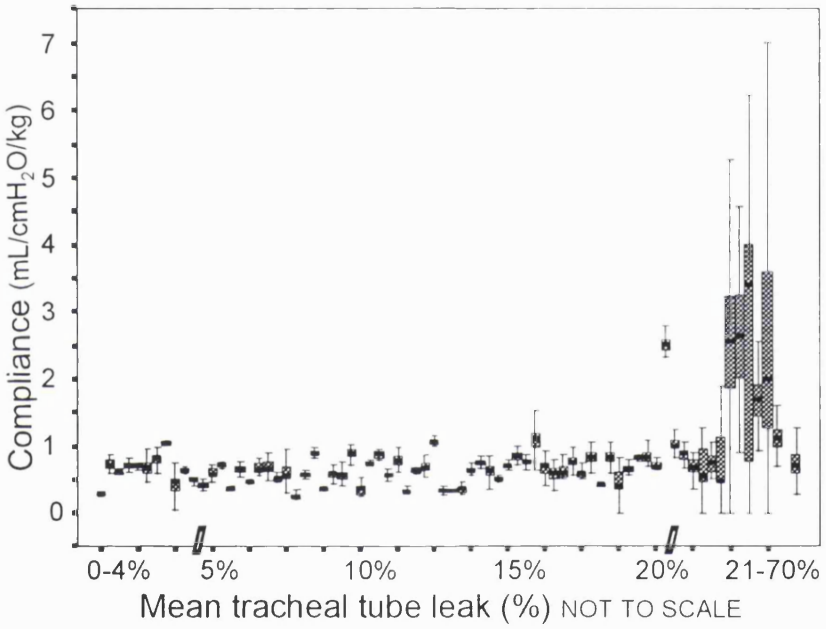


Each data point represents the mean value from one minute of recording from a 7 week old infant receiving pressure controlled ventilation (Bear Cub BP2001). Effective expired tidal volume was three times higher following tube change and reduction of leak. Note the gross overestimation and greater variability of calculated C_{rs} and R_{rs} in the presence of a large leak.

It can be seen that the reduction in tracheal tube leak from over 80% to an average of 16% was accompanied by a marked reduction in both the magnitude and variability of C_{rs} and R_{rs} (Figure 5-14). Nevertheless, even within the smaller range of leak that occurred after the tracheal tube had been changed (11 - 23%) there was still a significant correlation ($r^2 = 0.84$) between calculated values of resistance and magnitude of leak (Figure 5-14).

In an attempt to identify the magnitude of leak that would preclude accurate measurements, the median and inter-quartile range of all values of weight corrected compliance for each of the 75 children studied were plotted against the mean leak in that child during the measurement period (Figure 5-15). Tracheal tube leaks greater than 20% were associated with a marked rise in both the absolute values and the variability of weight corrected compliance. A similar pattern was obtained when resistance data were plotted in the same way.

Figure 5-15: Median and interquartile range of C_{rs} at different tracheal tube leaks



5.2.1.3 Discussion

These results confirm in vivo those of previous in vitro lung model studies which show that compliance and resistance values are overestimated in the presence of tracheal tube leak (Kuo et al. 1996; Kondo et al. 1997; Pyon et al. 1999; Pyon et al. 2000). Establishing how much leak is acceptable in a ventilated child depends very much on the clinical status of the child. The results from the current study suggest that a minimal leak (<20%) is essential if parameters of respiratory function are to be used as objective outcome measures, particularly if such measures are required to detect within-subject changes in response to therapeutic interventions. The work described in 5.2.1 has been accepted for publication in Intensive Care Medicine and is inserted in section 8.2 at the end of this thesis (Main et al. (a) 2001).

During ventilation, leak magnitude reflects both overestimation of V_{TI}, much of which having passed through the flow-meter will leak out around the tube before entering the child's lungs, and the reduction in V_{TE}. Kondo et al. found that leak during expiration was smaller and hence that V_{TE} was likely to be more accurate than V_{TI} (Kondo et al., 1997). For this reason, V_{TE} was used in preference to V_{TI} in all calculations during subsequent analyses.

Detailed discussion of the issues surrounding tracheal tube leak and interpretation of respiratory function monitoring in ventilated children will follow in 8.2, but based on the information available from the tracheal tube leak analysis, a decision was made to exclude children with tracheal tube leaks >20% from data analysis. In addition, change in leak during the measurement period was minimised by ensuring that the child's posture and head position were similar before and after treatment.

5.2.2 Normal variability of parameters

5.2.2.1 Effect of disconnecting the flow sensor

Although it had been established that normal variability of respiratory parameters in paralysed ventilated subjects was minimal, there was some concern that disconnection and reconnection of the flow sensor, as required for each physiotherapy treatment or nursing suction, would introduce a degree of additional variability, which would confound results.

5.2.2.1.1 Method

During quiet clinical periods, in which minimal clinical interventions were performed, baseline data were obtained for 15 minutes in 10 patients who were recruited into the pilot study. The flow sensor was then removed from the ventilator circuit for 3 minutes, before being returned to the circuit for a final 15 minutes. The mean difference in selected respiratory parameters before and after disconnection was compared to the mean change following physiotherapy and nursing suction for those 10 patients. Additional arterial blood gases were not taken prior to and following disconnection, hence data for these parameters were not available for comparison.

5.2.2.1.2 Results

The 95% confidence intervals of differences in respiratory parameters after disconnection are summarised in Table 5-1. Data summarising the effect of physiotherapy and nursing suction in the same 10 patients are also shown for comparison. Graphic representations of selected parameters are shown in Figure 5-16.

Table 5-1: Effect of disconnecting the flow sensor compared with physiotherapy treatment and nursing suction.

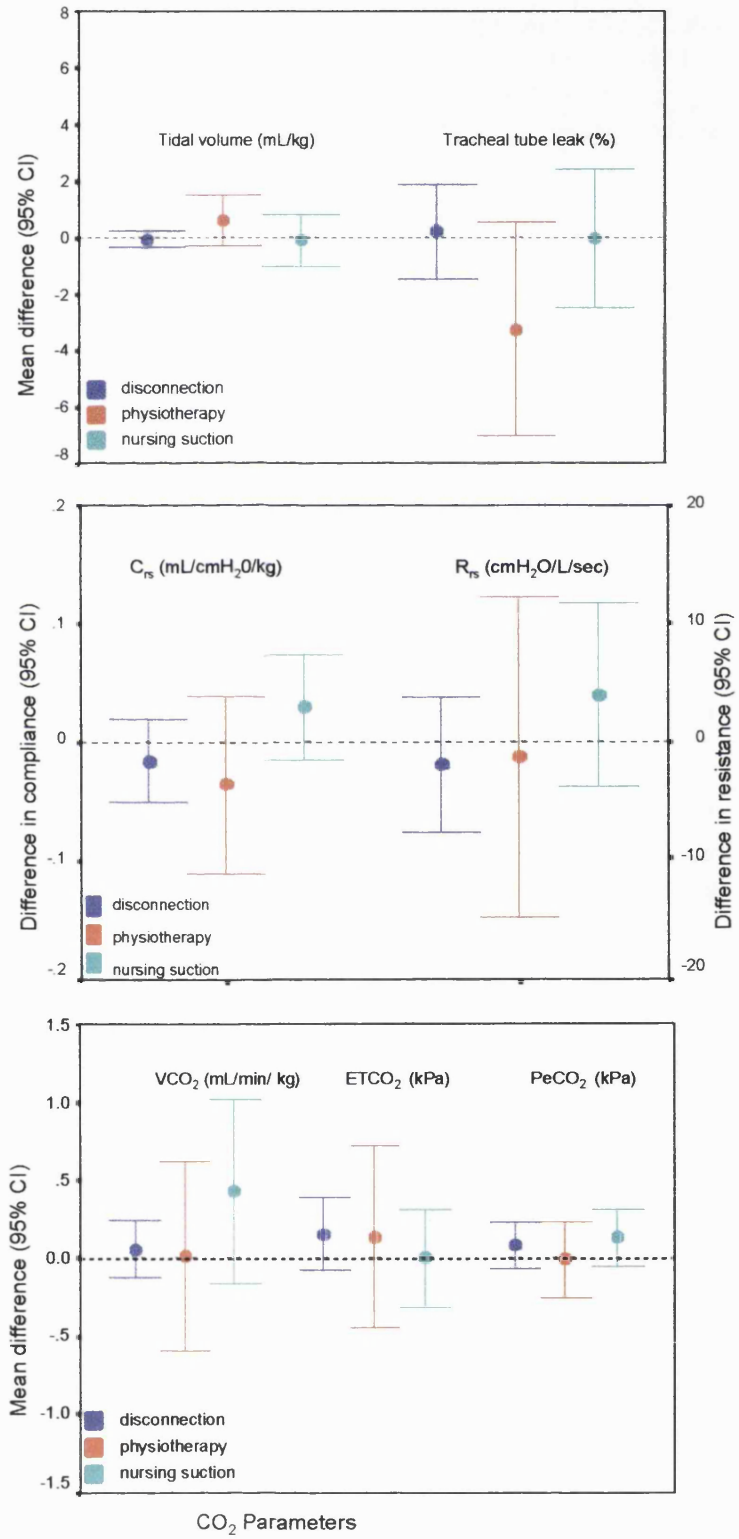
Outcome	†*Disconnection*	†*Physiotherapy*	†*Nursing suction*
V_{TE}/kg (mL/kg)	-0.40 to 0.19	-0.80 to 1.04	-1.49 to 0.33
C_{rs} (ml/cmH_2O/kg)	-0.07 to 0.02	-0.11 to 0.04	-0.02 to 0.05
R_{rs} (cm$H_2$0/L/sec)	-11.6 to 3.80	-12.2 to 14.8	-3.68 to 7.72
$ETCO_2$ (kPa)	-0.08 to 0.39	-0.45 to 0.71	-0.31 to 0.32
$PeCO_2$ (kPa)	-0.07 to 0.23	-0.25 to 0.23	-0.06 to 0.31
VCO_2 (mL/min/kg)	-0.13 to 0.24	-0.60 to 0.61	-0.17 to 1.02
Tube leak (%)	-2.37 to 2.50	-7.06 to 0.54 *	-1.86 to 1.47
Respiratory rate (breaths/min)	-0.05 to 0.05	-0.19 to 0.12	-0.24 to 0.59
PIP (cmH_2O)	-0.15 to 0.10	-0.48 to 1.40	-2.07 to 1.11
PEEP (cmH_2O)	-0.04 to 0.05	-0.60 to 0.24	-0.20 to 0.68
MAP (cmH_2O)	-0.05 to 0.04	-0.11 to 0.14	-0.08 to 0.22
PEF (L/min)	-0.24 to 0.54	-0.43 to 1.06	-1.12 to 0.24
t_I (seconds)	-0.02 to 0.01	-0.02 to 0.07	-0.07 to 0.02
t_E (seconds)	-0.03 to 0.06	-0.11 to 0.20	-0.32 to 0.12

†Results are expressed as 95% CI of the difference (after - before) between data during disconnection, physiotherapy and nursing suction. * *(p<0.09)*

There were no significant changes in any parameters which were associated with disconnection alone. The tendency for tracheal tube leak to decrease after physiotherapy will be discussed in 6.5.1. Although 10 patients were a relatively small group in which to examine the effect of disconnection alone, the confidence intervals of the mean

differences were small and provided some confidence that there were no systematic errors associated with disconnection of the flow sensor.

Figure 5-16: Difference (after - before intervention) in selected parameters in 10 patients after disconnection, physiotherapy or nursing suction



From Figure 5-16 it can be seen that for all parameters, the mean difference after disconnection was negligible and the confidence intervals of the difference were smaller for disconnection than they were for either of the treatment interventions. From these data it was concluded that disconnection of the flow sensor did not constitute a threat to evaluation of treatment effect.

5.2.2.2 Establishing potential perimeters for clinical significance

In the absence of published data demonstrating effects of physiotherapy or nursing suction on respiratory function in ventilated children, it was difficult to decide what magnitude of change in individuals would constitute clinical significance. It was therefore decided to determine the variability of individual respiratory parameters in the absence of interventions so that reasonable limits could be established for treatment related changes which were significantly larger than the limits for normal variability.

5.2.2.2.1 Method

Data were obtained from 33 randomly selected patients in the study population in whom there were two consecutive 15 minute periods without clinical interventions. The mean values of selected respiratory parameters in the consecutive time periods were compared, to assess normal variability of individual parameters during quiet clinical periods. The percentage difference and 95% LA in respiratory parameters between time periods were calculated for each parameter.

5.2.2.2.2 Results

The mean values, 95% CI, percentage change and 95% LA are presented in Table 5-2.

Table 5-2: Repeatability of measurements in 33 individuals in the absence of any interventions

Parameter	*15 mins (a)*	*15 mins (b)*	*95% CI (b-a)*	*mean % change (95% LA)*
V_{TE}/kg (mL/kg)	8.43 (2.21)	8.45 (2.29)	-0.07 to 0.11	0.13 (-5.3 to 5.5)
R_{rs}(cmH_2O/L/sec)	98.9 (67.2)	96.7 (69.2)	-4.15 to 6.35	-2.31 (-15.3 to 10.7)
C_{rs} (mL/cmH_2O/kg)	0.67 (0.26)	0.68 (0.26)	-0.01 to 0.02	1.09 (-7.1 to 4.9)
VCO_2 (mL/min/kg)	3.53 (1.08)	3.58 (1.08)	-0.03 to 0.14	0.69 (-6.2 to 7.6)
$ETCO_2$ (kPa)	5.25 (1.41)	5.26 (1.37)	-0.05 to 0.06	0.35 (-6.0 to 6.7)
$PeCO_2$ (kPa)	2.47 (0.80)	2.49 (0.79)	-0.03 to 0.04	-1.07 (-6.6 to 8.8)
Tube leak (%)	10.2 (4.58)	9.91 (4.80)	-1.16 to 0.65	-1.67 (-5.2 to 4.7)
Respiratory rate (breaths/min)	21.6 (4.55)	21.6 (4.33)	-0.24 to 0.21	0.17 (-5.3 to 5.0)
PIP (cmH_2O)	21.7 (2.07)	21.7 (1.95)	-0.32 to 0.21	-0.59 (-4.0 to 5.1)
PEEP (cmH_2O)	4.68 (0.97)	4.67 (0.98)	-0.03 to 0.01	-0.07 (-2.6 to 2.5)
MAP (cmH_2O)	9.16 (1.83)	9.16 (1.84)	-0.06 to 0.05	-0.19 (-3.8 to 4.2)
PEF (L/min)	9.17 (5.88)	9.17 (5.76)	-0.14 to 0.10	-0.02 (-5.6 to 7.0)
t_I (seconds)	0.86 (0.64)	0.86 (0.63)	-0.02 to 0.00	0.28 (-4.1 to 3.5)
t_E (seconds)	1.98 (0.13)	1.99 (0.14)	-0.03 to 0.04	0.19 (-6.2 to 5.8)

Results are expressed as mean(SD). 95% LA were calculated as: mean % difference ± $2xSD_{(\%\ difference)}$

The mean values for all respiratory parameters were not significantly different over the two time periods, and the small confidence intervals encompassing zero indicated highly reproducible data. Within subject variability of all parameters in Table 5-2 was minimal, with CV less than 5% in all cases and <2% in over half of them. The 95% limits of agreement were less than 10% for all parameters except R_{rs}. From this it could be assumed that changes in any parameters following therapeutic interventions which

exceeded ± 10%, (or ±20% for R_{rs}) within individual subjects were statistically significant changes which had the potential to be clinically important.

5.2.3 Deadspace measurements

A software problem relating to the automated calculation of deadspace by the "CO_2SMO Plus" program was discovered approximately 9 months after data collection had begun. At this stage approximately 48 patients had been studied. At times, the $PaCO_2$ values entered by the investigator were "rounded up" or "rounded down" in a rather random and inaccurate fashion. For example, a $PaCO_2$ of 5.78 kPa may have become 5.7 kPa, while 5.01 kPa may have become 5.2 kPa. Attempts to correct for this by entering a single decimal $PaCO_2$ value were not always successful, for example entering 5.8 kPa resulted in the software changing this to 5.9 kPa. The potential consequences of this problem were that by "rounding up" a pre-treatment $PaCO_2$ value while "rounding down" a post-treatment value, the change in deadspace may not have been reflected in the calculated value. At worst, the deadspace may have been shown to increase or decrease when in fact the opposite was true. This rounding error did not occur in all instances, but in approximately 1 in 4 blood gas entries.

After this problem was discovered, manual deadspace calculations were used when $PaCO_2$ values were inappropriately altered. However, there were concerns that affected deadspace data collected prior to this discovery would be unacceptable. To confirm that it was reasonable to accept the early calculations, deadspace calculations from the "CO_2SMO Plus" software were compared to manual calculations using the original blood gas values. Fifty paired blood samples were used in this comparison, 25 taken before and 25 after treatment. The samples were selected such that at least one of each paired sample was influenced by the $PaCO_2$ rounding error described above.

Differences in $PaCO_2$, V_D/V_T and $V_{D_{phys}}$ after treatment were calculated and manual calculations (using original blood gas values) were compared with the "CO_2SMO Plus" calculation in each case. When comparing $PaCO_2$ and V_D/V_T, in 22 of 25 cases the direction of change following treatment was the same by both manual calculation and the automated "CO_2SMO Plus" calculations. In the remaining 3 cases no change

following treatment was recorded by the "CO_2SMO Plus" CO_2 values while very small (±0.03 kPa) changes were suggested by the original $PaCO_2$ values. A standardised t-test of the paired differences showed no significant difference between the "CO_2SMO Plus" and manual calculations ($p = 0.34$ and 0.38 for $PaCO_2$ and $V_{D_{phys}}/ V_T$ respectively). When $V_{D_{phys}}$ was compared using both methods of calculation, the direction of change following treatment was the same in all 25 cases, and the t-test revealed no significant difference between the paired samples ($p = 0.90$). As a result of this exercise, it was felt that early recordings of blood gas values would yield an accurate reflection of change following treatment if not precisely accurate absolute values. In addition, the fact that the rounding error occurred intermittently meant that the majority of the affected blood gases had been corrected within this exercise. During final analysis, $PaCO_2$ and deadspace values were calculated with and without the early blood gas values and no differences in significance were found.

6. Results

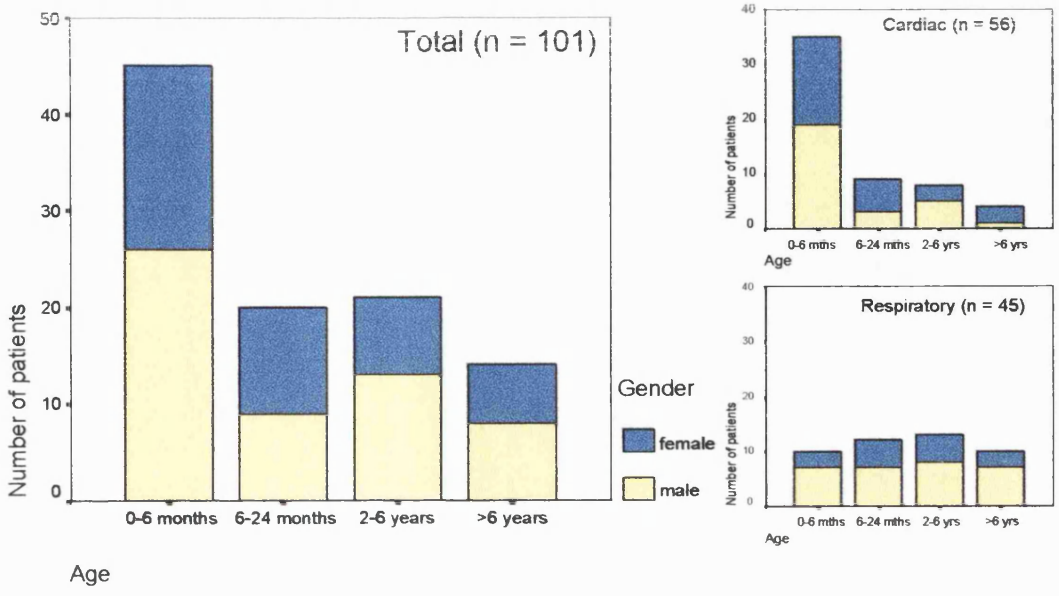
6.1 Study population demographics

One hundred and one infants and children were recruited into the study (median age: 9 months, range 3 days - 16yrs). Distribution of age and weight in the study population are shown in Figure 6-1 and Figure 6-2. The majority of patients studied (60%) were under 1 year old, most of whom (59%) were less than 3 months old.

Of the 101 patients, 56 had a primary cardiac diagnosis (median age: 8 weeks, 3 days - 16 years, median weight 3.95kg, range: 2 - 37kg) and 45 had primary or secondary respiratory problems (median age 22 months, range: 3 days - 16 years, median weight 10.1kg, range 2.7 - 87kg).

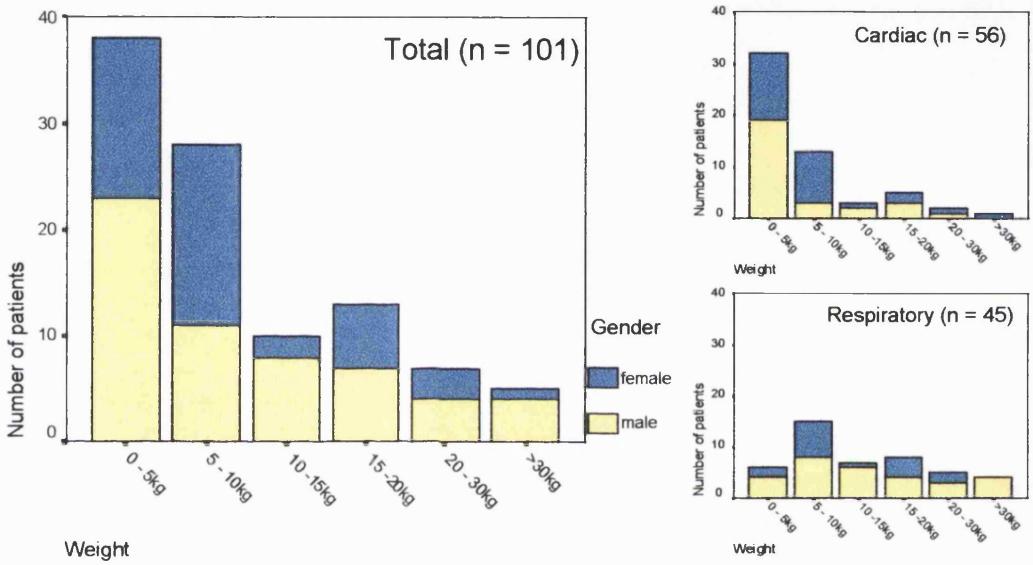
Eleven of 101 patients (11%) were excluded from analysis because of mean tracheal tube leak in excess of 20% during the measurement period. Their exclusion did not substantially change the median age or weight of either group. In the 90 remaining patients, 52 had cardiac problems and 38 had respiratory problems.

Figure 6-1: Ages of study patients



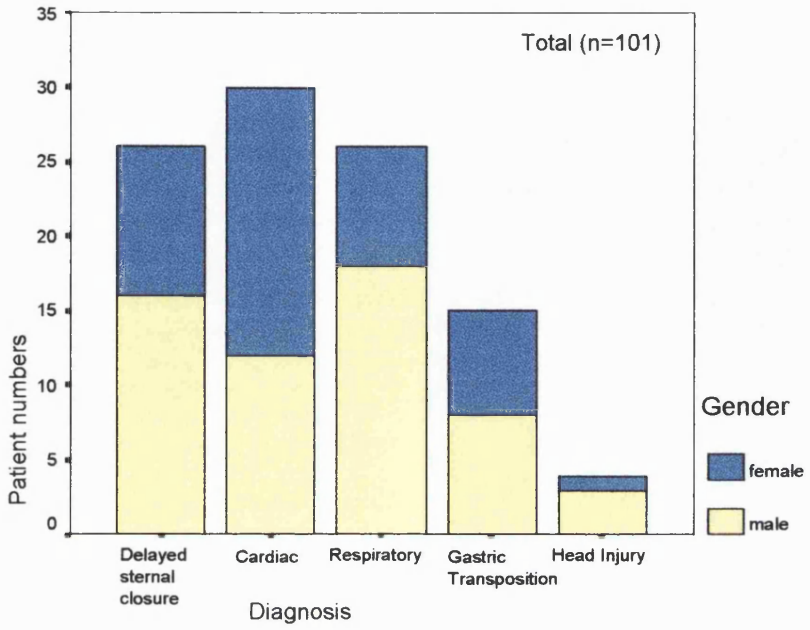
There were 28 males and 28 females in the primary cardiac group while only 16/45 in the respiratory group were female. This may reflect the increased susceptibility of males to respiratory disease in early life (Gold et al. 1994; Hibbert et al. 1995; Dezateux and Stocks, 1997).

Figure 6-2: Body weight of children in study.



The cardiac group included those who had delayed sternal closure following cardiac surgery, results from whom have been reported in a separate paper (section 8.1) accepted for publication by Critical Care Medicine (Main et al. (b) 2001). Secondary respiratory problems included children with head injuries and those undergoing elective surgical procedures such as gastric transposition. Both groups included medical and surgical patients. Broader diagnostic groups are illustrated in Figure 6-3.

Figure 6-3: Diagnostic groups of children in study.



The majority of patients with primary cardiac problems were ventilated with a pressure controlled mode and few with volume controlled mode, while ventilation mode in the respiratory group was more evenly spread (Figure 6-5 to Figure 6-7). This feature is probably related more to age than diagnosis, since the median age in the cardiac group was significantly lower than that of the respiratory group (Figure 6-4).

Figure 6-4: Ventilation mode for different age groups and diagnoses

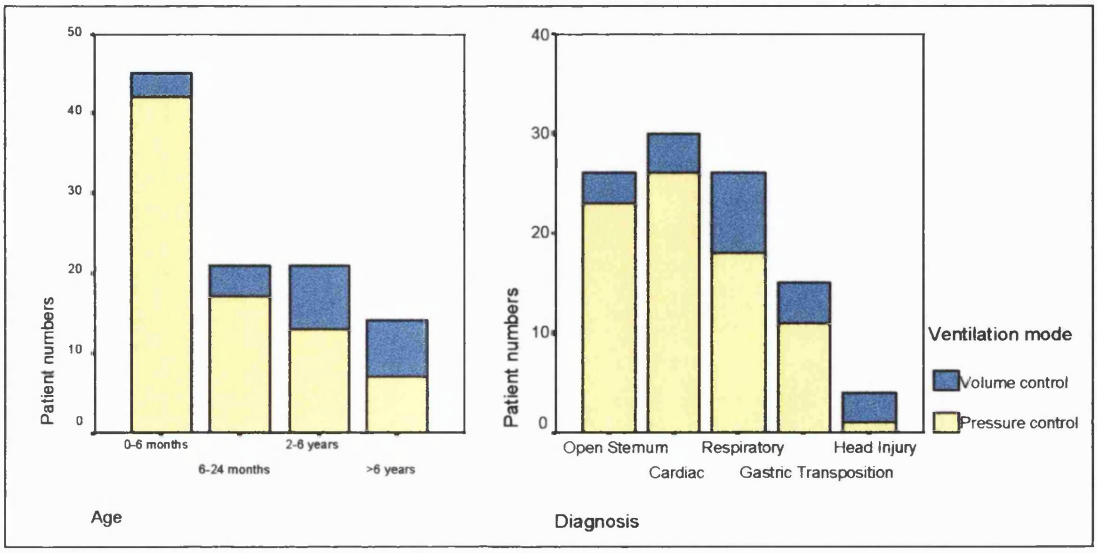


Figure 6-5: Chart of patients receiving physiotherapy treatments

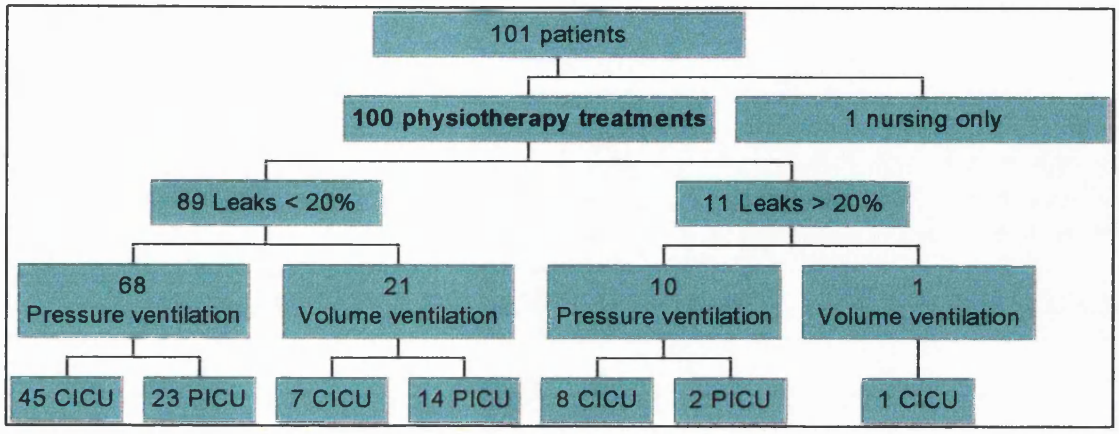


Figure 6-6: Chart of patients receiving nursing suction

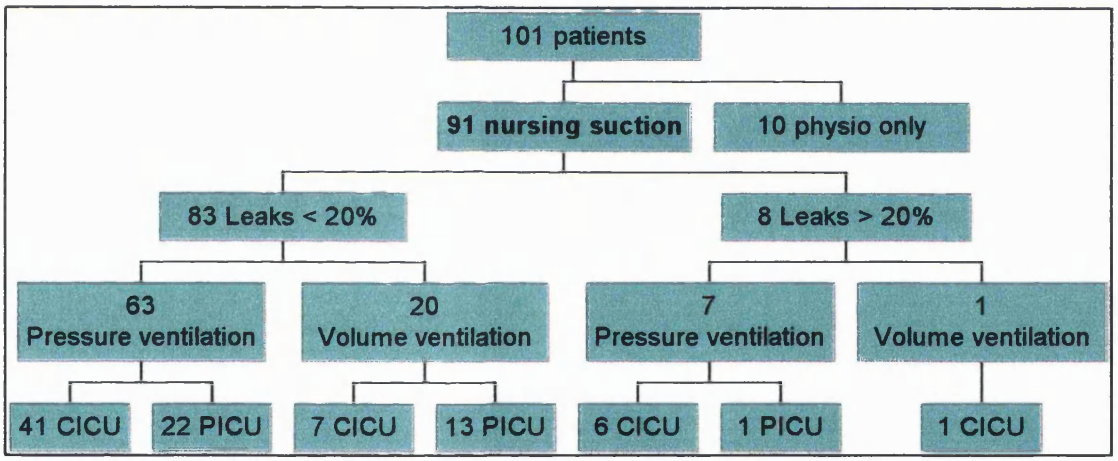
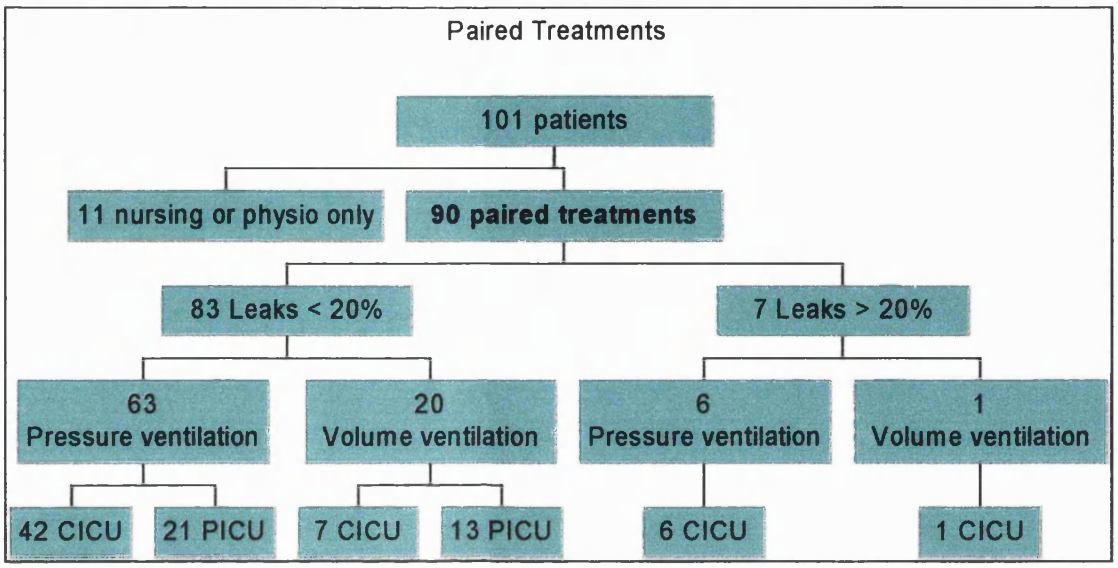


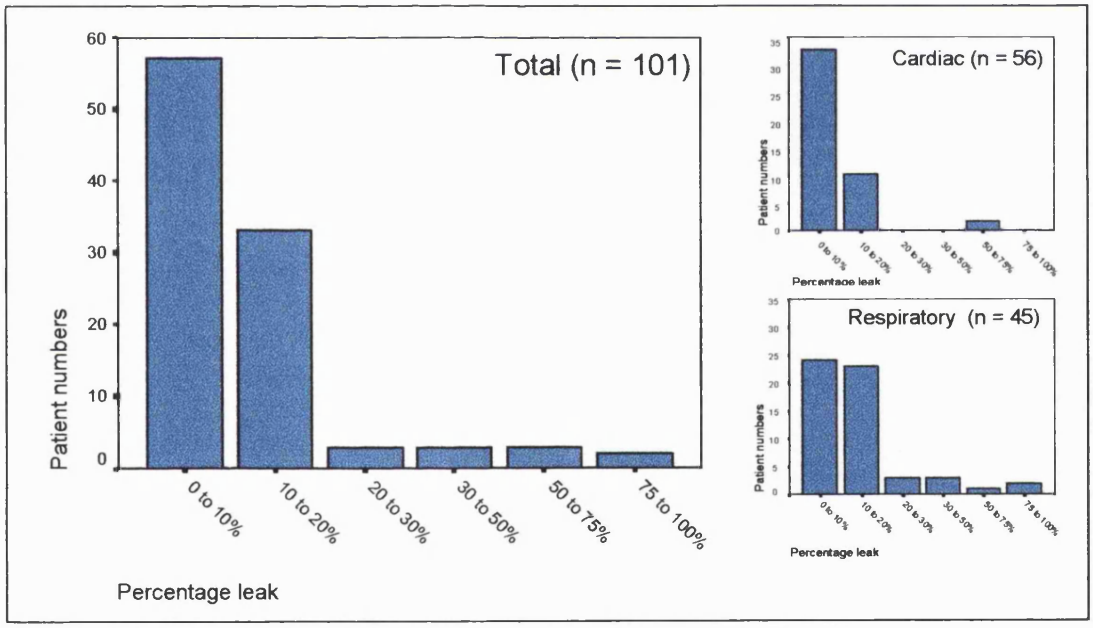
Figure 6-7: Chart of patients receiving both physiotherapy and nursing suction



6.1.1 Tracheal tube leak

The majority of children in the study were <8 years of age and were therefore ventilated via uncuffed tracheal tubes. The decision was made in the revised protocol to exclude patients with tracheal tube leak >20%, because of the influence of leak on V_{TE} as well as the consequent gross errors in C_{rs} and R_{rs} calculations (section 5.2.1). However, residual influences of tracheal tube leak in the remaining patients could have potentially jeopardised interpretation of results, albeit in a more subtle way. To prevent changes in respiratory function from being erroneously attributed to treatment effect, the influence of tracheal tube leak as co-variable was constantly taken into account throughout analysis of data. Figure 6-8 illustrates the magnitude and situation of tracheal tube leaks encountered in the study population.

Figure 6-8: Magnitude of tracheal tube leaks in study population



Eleven patients (10.9%), seven of whom had received paired treatments were excluded from analysis due to large tracheal tube leaks during the measurement period. Details of the magnitude and variability of leaks in these patients are shown in Table 6-1.

Table 6-1: Details of tracheal tube leak during data collection in 11 patients excluded from analysis

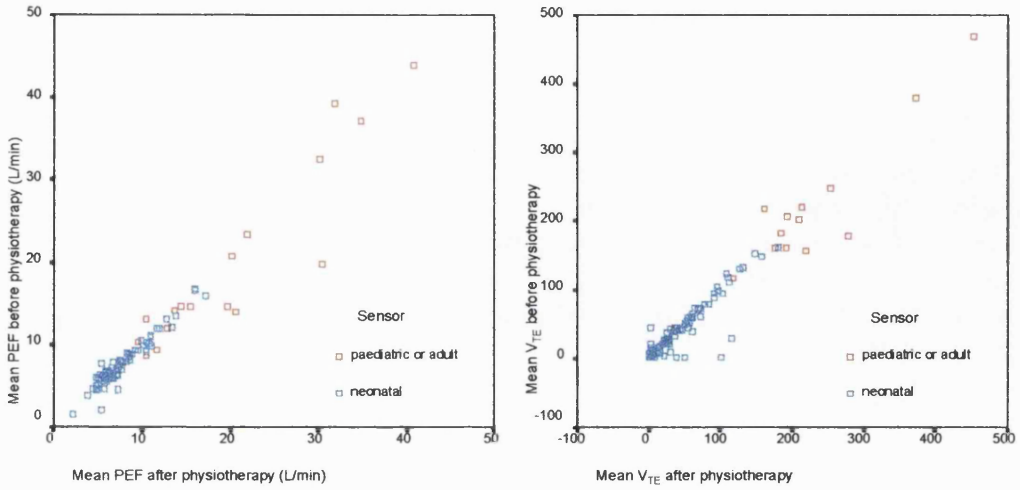
Patient	*Mean (SD)*	*min (%)*	*max (%)*	*Median (IQR)*
1	21.6 % (4.9)	11.4	66.4	20.4 % (19.3 - 24.1)
2	21.9 % (3.0)	17.5	61.0	21.6 % (20.6 - 22.8)
3	22.9 % (5.2)	9.4	76.9	22.4 % (20.5 - 25.0)
4	23.3 % (2.7)	13.9	34.5	23.1 % (21.6 - 24.3)
5	26.3 % (23.5)	2.3	94.3	13.4 % (10.2 - 55.9)
6	31.5 % (11.2)	4.6	69.8	35.5 % (19.9 - 41.2)
7	35.2 % (20.5)	10.0	70.7	28.7 % (15.3 - 57.3)
8	58.8 % (17.6)	10.4	91.2	61.0 % (50.1 - 68.9)
9	61.5 % (34.7)	5.0	97.2	86.6 % (19.5 - 89.7)
10	63.6 % (12.1)	24.9	69.6	66.4 % (57.7 - 69.6)
11	65.1 % (16.2)	25.7	97.6	61.5 % (51.0 - 76.0)

IQR refers to the inter-quartile range

6.1.2 Ranges of peak expiratory flow and V_{TE} in the study population.

In section 3.1.1, the linear range of the neonatal and paediatric or adult flow sensors was assessed and found to be 0.75 - 28L/min, and 10 - 55L/min respectively. To confirm that appropriate sensors were selected for the study population, the ranges of peak flow and tidal volumes encountered during measurements were reviewed. The flow range encountered in the study population (Figure 6-9) was compared to the linear range for each flow sensor to establish whether any sensor was likely to have produced inaccurate recordings for particular individuals. From Figure 6-9, it can be seen that the flows and volumes were within linear range for each of the sensors selected.

Figure 6-9: Flow and volume range in the study population



Patients studied with the neonatal flow sensor were ventilated with flows between 1.5 and 20 L/min (V_{TE}: 4.5 to 180mL): well within the limits of accuracy for the neonatal flow sensor. These patients included those on ECMO who were ventilated with very low flow and tidal volumes.

The clinical flow range for which the paediatric flow sensor was used was within the linear range of the sensor. Patients measured using the paediatric or adult flow sensors, were ventilated in the flow range 10 - 45L/min and tidal volumes measured were >40mL.

6.2 Randomisation

Although every attempt was made to randomise patients into treatment groups (by witnessed coin toss at the bedside), this was not always possible. Sometimes, by the time recruitment and consent had been achieved and equipment had been set up, nursing or physiotherapy staff may have been planning and were about to execute a treatment. In these instances, when it was diplomatically difficult to insist upon randomisation, (since the staff member concerned would have assessed their treatment to be clinically necessary), whichever treatment was imminent was then recorded as the first treatment. The alternative treatment was then performed as usual later on in the day. Such non-random treatments due to opportunistic recruitment occurred intermittently throughout the course of the study and involved both 'nursing first' and 'physiotherapy first' occurrences. Of the 89 patients included in analysis, 60 were randomised while 29 were opportunistically recruited. Of the 60 randomised patients, 27 had physiotherapy first and 33 had nursing suction first. In the non-random group, 19 had physiotherapy first,

while 10 patients had nursing suction first. In total, 46 patients received physiotherapy first and 43 nursing suction first.

All results were analysed with and without the non-randomised group, but no differences were found for outcome in any parameters. Thus all non-randomised patients were included in analysis, provided other inclusion criteria were satisfied.

6.3 Physiotherapy and nursing treatment details

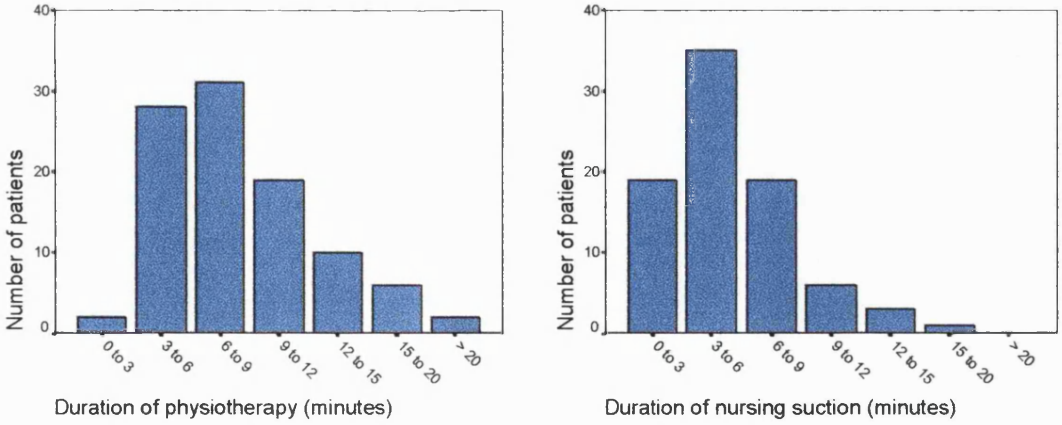
Figure 6-10 to Figure 6-12 illustrate the differences between physiotherapy treatments and nursing suction. In general physiotherapy treatments were significantly longer, involved more saline instillation and the use of more suction catheters (Table 6-2).

Table 6-2: Differences between paired physiotherapy (p) and nursing suction (n) treatments.

	Physiotherapy	*Nursing suction*	*95% CI of the difference (n-p)*	*P*
Duration of treatment (minutes)	8.5 (3.5)	5.6 (2.7)	-3.76 to -1.88	< 0.0001
Total tracheal saline instillation (mL)	3.6 (2.4)	1.8 (1.6)	-2.37 to -1.30	< 0.0001
Total number of catheters used	3.2 (1.3)	2.7 (1.4)	-0.80 to -0.15	0.004

Results are expressed as mean (SD)

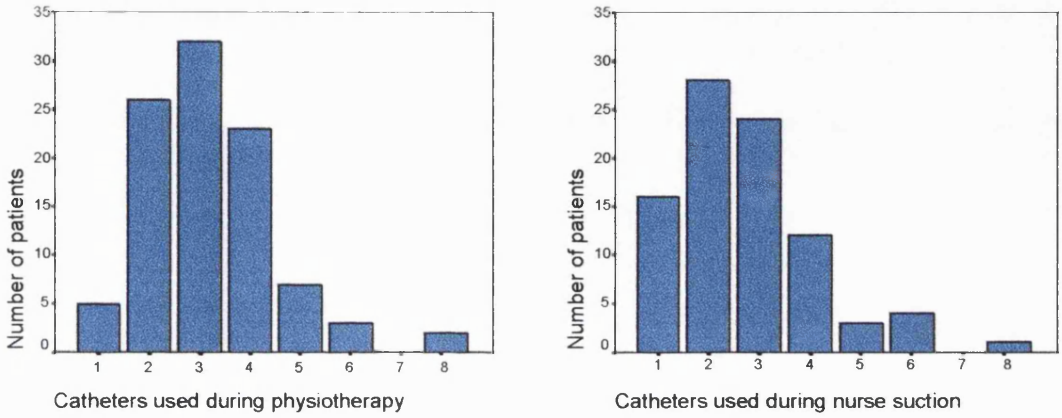
Figure 6-10: Duration of physiotherapy and nursing treatments.



Duration of treatment was not influenced by diagnosis or age and did not appear to be influenced by sputum yield for nurses or physiotherapists. When data pairs were examined (data from patients who had received both nursing suction and physiotherapy), physiotherapy treatments were significantly longer 8.5 (3.5) minutes against 5.6 (2.7)

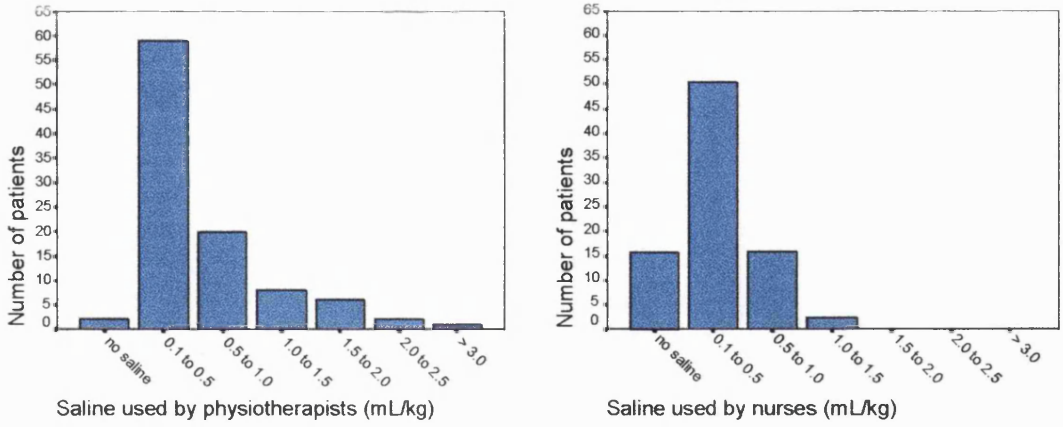
($p < 0.0001$). While 96% of nursing suction treatments were completed in less than 12 minutes, only 80% of physiotherapy treatments were completed in the same time.

Figure 6-11: Suction catheters used per treatment by physiotherapists and nurses.



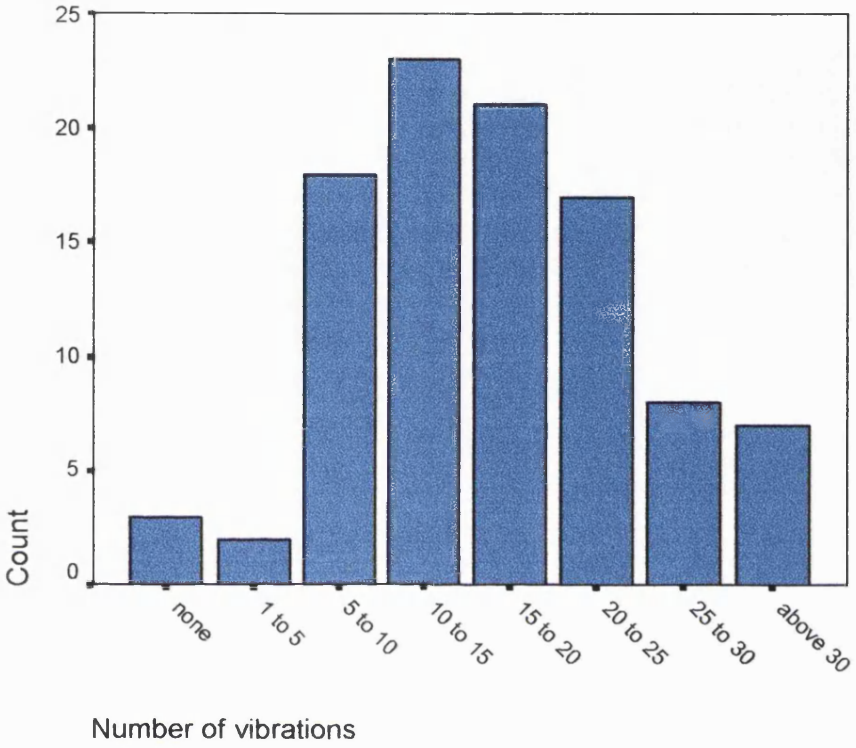
There were small differences in numbers of catheters used per treatment. Physiotherapists were most likely to use three catheters per treatment, whereas nurses most frequently used two. Physiotherapists were much less likely than nurses to use a single catheter in any treatment.

Figure 6-12: Saline instilled per treatment by physiotherapists and nurses.



Although 0.1 - 0.5 mL/kg was the preferred volume of saline per treatment for both nurses and physiotherapists, nurses were more likely not to use any saline in some treatments. While nurses never exceeded saline volumes of 1.5 mL/kg in this study, physiotherapists did so in 10% of the treatments.

Figure 6-13: Number of chest wall vibrations performed during physiotherapy treatment.



Physiotherapists used a median number of 18 chest wall vibrations per treatment (range 0 - 55). Number of vibrations did not appear to be influenced by age or diagnosis.

6.3.1 Sputum yield and adverse events

Sputum yield from treatments was reported as "small", "medium" or "large" 40%, 45% and 15% of the time by nurses and 28%, 48% and 24% of the time by physiotherapists. Adverse events such as desaturation or drop in blood pressure were reported on 13/91 (14%) occasions during nursing suction and 8/100 (8%) occasions during physiotherapy but these events were not influenced by diagnosis or age. Treatment duration, adverse events and volume of saline instillation might more reasonably be related to severity of illness or haemo-dynamic stability, factors which were not examined in this study.

6.4 Ventilation parameters during data collection intervals

Patients were only recruited into the study if they were paralysed or so heavily sedated that spontaneous ventilatory effort was not possible. Despite protocol requirements for ventilation to remain unchanged throughout the measurement period, inadvertent changes in ventilator settings would have had the potential to confound results. To confirm that ventilatory parameters remained constant before and after treatment and that changes in respiratory function were due to treatment effect alone, mean values of fundamental ventilatory parameters were compared (Table 6-3). In addition ventilatory parameters were scanned to identify individual changes in ventilator settings >10%. None were discovered.

Table 6-3: Recordings of ventilatory parameters during measurement periods

Parameter	*Treatment*	*N*	** Before treatment (B)*	** After treatment (A)*	*95% CI (A-B)*	*p*
Respiratory rate (breaths/min)	physio	89	21.5 (4.87)	21.5 (5.00)	-0.23 to 0.15	0.70
	nursing	83	22.1 (5.01)	21.9 (5.22)	-0.08 to 0.33	0.24
PIP (cmH_2O)	physio	89	22.7 (3.68)	22.4 (3.90)	-0.60 to 0.10	0.16
	nursing	83	22.6 (3.61)	22.5 (3.40)	-0.27 to 0.18	0.70
PEEP (cmH_2O)	physio	89	5.86 (1.80)	5.90 (1.80)	-0.03 to 0.10	0.25
	nursing	83	5.92 (1.83)	5.93 (1.87)	-0.06 to 0.09	0.77
MAP (cmH_2O)	physio	89	10.9 (2.76)	10.9 (2.74)	-0.11 to 0.07	0.60
	nursing	83	11.0 (2.65)	11.0 (2.65)	-0.09 to 0.03	0.30
PEF (L/min)	physio	89	10.0 (7.37)	10.2 (7.08)	-0.20 to 0.61	0.32
	nursing	83	10.3 (8.10)	10.2 (7.11)	-0.36 to 0.33	0.93
t_I (seconds)	physio	89	0.96 (0.24)	0.95 (0.23)	-0.03 to 0.01	0.25
	nursing	83	0.97 (0.26)	0.97 (0.25)	-0.01 to 0.02	0.71
t_E (seconds)	physio	89	2.05 (0.59)	2.05 (0.62)	-0.03 to 0.05	0.74
	nursing	83	2.04 (0.62)	2.06 (0.61)	-0.06 to 0.01	0.16

** Results are expressed as mean (SD).*

Whether analysed as a whole group, or as separate sub-groups (pressure or volume controlled ventilation), mean values of ventilation parameters before treatment were not significantly different from those following treatment (Table 6-3). The single exception to this was peak inspiratory pressure (PIP) when analysis was performed on the volume controlled ventilation group alone. In this group, there was a trend for PIP to decrease after physiotherapy ($p<0.08$) which was persistent after 30 minutes ($p<0.03$). Since patients on VCV have a set volume delivered on each breath and pressure required for delivering the volume depends on underlying respiratory mechanics, the pressure change in this group was likely to reflect underlying changes in respiratory function as a result of treatment. The stability of ventilation parameters during the measurement intervals confirmed that these potential variables were not likely to influence outcomes when examining physiotherapy and nursing suction treatment effects.

6.5 The effect of physiotherapy and nursing suction.

Having established the differences in techniques between nursing suction and physiotherapy (section 6.3), standardised t-tests were used to compare data before and after treatment to investigate the effects of physiotherapy and nursing treatments and then to investigate statistical differences between the two methods. These tests were initially performed on all patients with tracheal tube leak <20% (n = 89 and 83 for physiotherapy and nursing treatments, respectively) and then repeated after splitting patients into groups of pressure or volume controlled ventilation (Figure 6-5 and Figure 6-6) to establish the effects, if any, of ventilation mode on treatment response. For parameters where concern existed about normal distribution of data (for example R_{rs}, $V_{D_{alv}}$), additional non parametric tests (Wilcoxon) were performed to confirm results. For parameters where concern existed about the influence of changes in tracheal tube leak, general linear model analyses were performed to separate treatment effect from tracheal tube leak effect. Analysis was therefore performed using data from 89 patients who had physiotherapy and 83 patients who had nursing suction (of whom 83 had both physiotherapy and nursing suction performed on the same day). A comparison of results from the 15-minute periods prior to and following physiotherapy are presented in Table 6-4, while the effects of nursing suction and comparison of these treatments are shown in Table 6-5 and Table 6-6 respectively.

Although the minimum data collection period prior to and following physiotherapy was 15 minutes, it was possible to continue measurements in some patients for up to 90 minutes after treatment. By continuing monitoring whenever possible, it was hoped that data from such patients would allow assessment of any delayed or more prolonged treatment effect. Details of these more prolonged effects are given below each table. Parameters measured included tidal volumes, CO_2 outcomes, respiratory compliance and resistance, arterial blood gases and deadspace measurements.

The difference in numbers between patients with $V_{D_{phys}}$, $V_{D_{alv}}$ and $V_{D_{phys}}/ V_T$, calculations and arterial blood gas values is by virtue of the fact that a small minority of patients had blood gases taken between 23 and 29 minutes after treatment (a little earlier than the 30 minute interval at which all other values were compared) because of some imminent significant clinical intervention. In these cases, we elected not to include the deadspace calculations since they represented comparison between values at different measurement intervals. In reality, it made no difference at all to the end result whether they were included or not.

Table 6-4: Effect of physiotherapy on respiratory function

Parameter	*N*	*before physio (B)*	*after physio (A)*	*95% CI (A-B)*	*mean % change*	*p*
Tube leak (%)	89	9.44 (6.95)	8.81 (7.03)	-1.36 to 0.10	-0.6	0.09 †
V_{TE}/kg (mL/kg)	89	8.27 (2.66)	8.36 (2.74)	-0.12 to 0.30	1.1	0.38
R_{rs} (cmH_2O/L/sec)	89	72.8 (63.2)	65.9 (45.0)	-14.2 to 0.39	-9.5	0.06 ‡
C_{rs} (mL/cmH_2O/kg)	89	0.67 (0.29)	0.68 (0.32)	-0.01 to 0.03	1.5	0.41
VCO_2 (mL/min/kg)	89	4.30 (1.58)	4.27 (1.50)	-0.15 to 0.08	-0.7	0.57
$ETCO_2$ (kPa)	89	5.10 (1.38)	5.04 (1.21)	-0.19 to 0.08	-1.8	0.39
$PeCO_2$ (kPa)	89	3.30 (1.83)	3.24 (1.78)	-0.14 to 0.01	-1.8	0.10††
$V_{D_{airway}}$/kg (mL/kg)	89	1.61 (0.54)	1.60 (0.55)	-0.05 to 0.03	-0.6	0.57
$V_{D_{alv}}$/kg (mL/kg)	75*	1.64 (1.03)	1.92 (1.32)	0.15 to 0. 41	17.1	**<0.001**
$V_{D_{phys}}$/kg (mL/kg)	75*	3.24 (1.34)	3.54 (1.60)	0.16 to 4.43	9.3	**<0.001**
$V_{D_{phys}}$/ V_T	75*	0.41 (0.14)	0.42 (0.14)	0.00 to 0.03	2.4	0.07
pH	80*	7.41 (0.09)	7.41 (0.08)	-0.01 to 0.01	0.0	0.95
$PaCO_2$ (kPa)	80*	5.30 (1.41)	5.22 (1.11)	-0.30 to 0.12	-1.5	0.39
PaO_2 (kPa)	80*	12.7 (4.81)	12.6 (5.80)	-1.16 to 0.96	-0.8	0.85
HCO_3- (mmol/L)	80*	24.8 (3.78)	24.4 (3.52)	-0.72 to -0.06	-1.6	**0.02**
Base Excess	80*	0.17 (4.21)	-0.18 (3.86)	-0.68 to -0.01	-206	**0.05**
O_2 Saturation (%)	80*	94.3 (7.62)	93.6 (8.02)	-1.26 to -0.07	-0.7	**0.03**

Results are expressed as mean (SD). Significant results are in bold type.
Of the 89 patients in whom data were collected for 15 minutes after physiotherapy, recordings were continued for 30 minutes in 75 patients, 45 minutes in 42 patients and 60 minutes in 26 patients. It was only possible to continue recording without significant clinical interventions in 14 patients at 75 minutes and 8 patients at 90 minutes.
† $p<0.09$ after 30 minutes, ‡ $p<0.06$ after 30 minutes, †† $p<0.05$ after 30 minutes.
All other parameters remained non-significant after longer time intervals.
**Data dependent on blood gas analyses were collected at discrete intervals immediately before physiotherapy and 30 minutes afterwards.*

Table 6-5: Effect of nursing suction on respiratory function

Parameter	*N*	*before nurse suction (B)*	*after nurse suction (A)*	*95% CI (A-B)*	*Mean % change*	*p*
Tube leak (%)	83	9.50 (6.77)	8.91 (6.60)	-1.35 to 0.18	-0.6	0.13
V_{TE}/kg (mL/kg)	83	8.47 (2.79)	8.31 (2.42)	-0.44 to 0.11	-1.9	0.23
R_{rs} (cmH_2O/L/sec)	83	73.5 (51.9)	72.3 (51.9)	-4.61 to 2.16	-1.6	0.47
C_{rs} (mL/cmH_2O/kg)	83	0.68 (0.28)	0.67 (0.30)	-0.03 to 0.01	-1.5	0.23
VCO_2 (mL/min/kg)	83	4.22 (1.18)	4.29 (1.31)	-0.06 to 0.19	1.7	0.30
$ETCO_2$ (kPa)	83	5.04 (1.44)	5.09 (1.26)	-0.05 to 0.16	1.0	0.32
$PeCO_2$ (kPa)	83	3.29 (1.93)	3.30 (1.86)	-0.05 to 0.07	0.3	0.72
$V_{D_{airway}}$/kg (mL/kg)	83	1.59 (0.55)	1.59 (0.53)	-0.03 to 0.03	0.0	0.96
$V_{D_{alv}}$/kg (mL/kg)	73*	1.73 (1.14)	1.74 (1.05)	-0.12 to 0.13	0.6	0.94
$V_{D_{phys}}$/kg (mL/kg)	73*	3.31 (1.46)	3.32 (1.32)	-0.13 to 0.14	0.3	0.95
$V_{D_{phys}}$/ V_T	73*	0.40 (0.14)	0.41 (0.13)	-0.01 to 0.02	2.5	0.27
pH	80*	7.42 (0.08)	7.41 (0.08)	-0.01 to 0.01	-0.1	0.47
$PaCO_2$ (kPa)	80*	5.20 (1.21)	5.25 (1.06)	-0.11 to 0.21	1.0	0.51
PO_2 (kPa)	80*	13.4 (6.39)	12.7 (4.79)	-1.41 to 0.17	-5.2	0.12
HCO_3- (mmol/L)	80*	24.7 (3.54)	24.9 (3.71)	-0.17 to 0.61	0.8	0.27
Base Excess	80*	0.13 (3.88)	0.23 (4.20)	-0.30 to 0.49	76.9	0.63
O_2 saturation (%)	80*	94.2 (7.14)	94.3 (7.29)	-0.60 to 0.80	0.01	0.78

Results are expressed as mean (SD). Of the 83 patients in whom data were collected for 15 minutes after nurse suction, recordings were continued for 30 minutes in 74 patients, 45 minutes in 49 patients and 60 minutes in 24 patients. It was only possible to continue recording without significant clinical interventions in 9 patients at 75 minutes. All changes in respiratory parameters remained non-significant after longer time intervals.

**Data dependent on blood gas analysis were collected at discrete intervals immediately before nursing suction and 30 minutes afterwards.*

6.5.1 Tracheal tube leak

From Table 6-4 there appeared to be a tendency for reduction in tracheal tube leak following physiotherapy ($p<0.09$). This effect was unlikely to be attributable to more proficient reconnection after treatment, since disconnection and reconnection alone did not suggest any such relationship (5.2.2.1). It was possible therefore that the change in leak was related to underlying changes in respiratory mechanics. However, tracheal tube leak, C_{rs} and R_{rs} have complex relationships with each other and a reduction in leak in the absence of any changes in physical connection would usually be associated with either an improvement in C_{rs} or reduction in R_{rs}. However, reduction in leak results in less overestimation of both C_{rs} and R_{rs} (5.2.1). The exclusion of patients with large leaks from this study increased the probability that the observed reduction in leak was associated with either a real improvement in C_{rs} (which was not evident from Table 6-4) or a real reduction in R_{rs} (possible from Table 6-4). Since even minor leaks may have confounded measurements of C_{rs} and R_{rs}, general linear model (GLM) analysis was performed to assess the covariant effect of change in tracheal tube leak during the measurement period.

When "change in leak" and "treatment effect" were explored as separate co-variables influencing C_{rs} and R_{rs} (SPSS, GLM: repeated measures), there was no evident physiotherapy effect on C_{rs} after treatment, but a significant within-subject effect of leak change ($p<0.05$). This effect was sustained at 30 minutes, and was persistent, even when excluding all patients with tracheal tube leak > 10%. By contrast, physiotherapy emerged as significantly influencing R_{rs} ($p<0.03$) while change in leak had no within-subject effect. Treatment effect remained significant at 30 minutes after physiotherapy. Nursing suction did not appear to have any influence on R_{rs}. It therefore appears that physiotherapy treatments may have reduced R_{rs}, which in turn reduced tracheal tube leak, and that this reduction in leak influenced C_{rs}.

When "change in leak" and "treatment effect" were explored as separate co-variables influencing V_{TE}, (GLM), there was no evident effect of either physiotherapy or leak (provided leaks >20% were excluded). Nursing suction, however tended to produce a

reduction in V_{TE} 15 minutes after treatment which was sustained after 30 and 45 minutes (6.5.2).

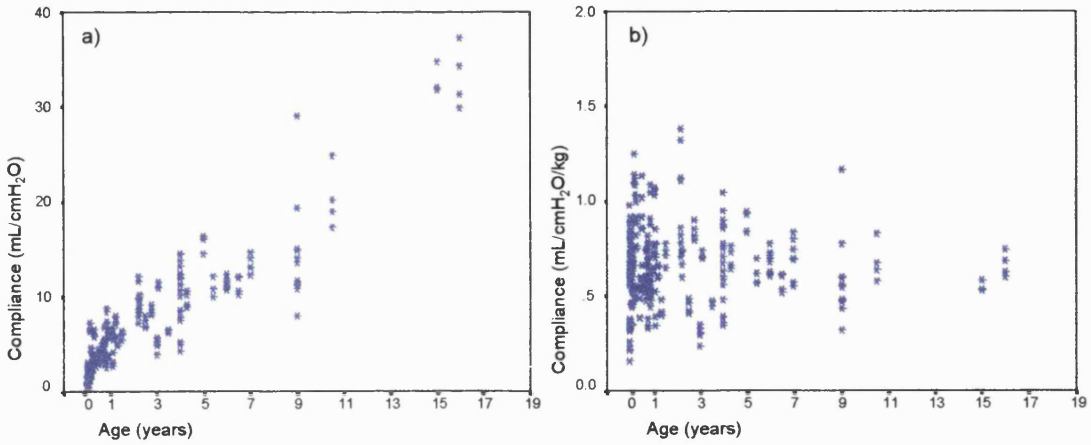
6.5.2 Tidal volume

From Table 6-4 and Table 6-5, it can be seen that univariate analysis of V_{TE} revealed no statistically significant group changes after either physiotherapy or nursing suction. This result remained consistent for physiotherapy even after GLM analysis was performed to explore the influence of leak as a covariant (6.5.1) and after analysis was split to explore the influence of different ventilation modes and diagnoses. However as discussed above, when GLM analysis was used to tease out the effect of nursing suction versus leak, there was a tendency for nursing suction to produce a reduction in V_{TE} ($p=0.08$). This tendency became statistically significant at 30 minutes ($p=0.04$, $n=63$) and 45 minutes ($p=0.02$, $n=48$). Whilst there were minimal group changes in V_{TE} after nursing suction or physiotherapy, there were significant changes in V_{TE} within individual children which will be discussed in 6.6.

6.5.3 Compliance

Age and weight are known to have important between-subject effects on compliance values, with C_{rs} increasing with increasing age and weight (Figure 6-14a). Thus C_{rs} calculations were expressed as weight corrected units (Figure 6-14b).

Figure 6-14: The difference between C_{rs} as a) absolute and b) weight corrected values against age.



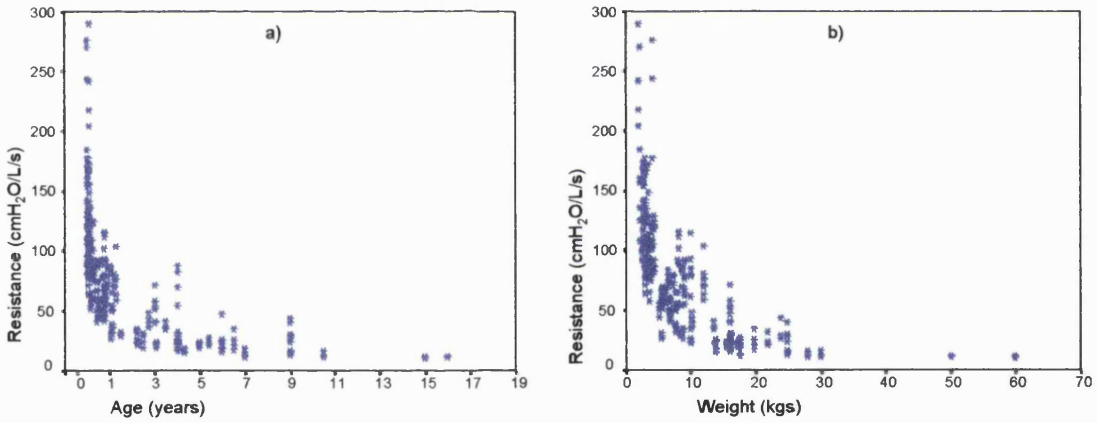
From Table 6-4 and Table 6-5, it can be seen that there were no significant group changes in C_{rs} as a result of physiotherapy treatment or nursing suction. This result

remained consistent for physiotherapy treatments when analysis was split to explore the influence of different ventilation modes. However there appeared to be a tendency for C_{rs} to fall after nursing suction in infants on pressure-controlled ventilation ($p= 0.07$, $n= 63$) and this change remained significant after 30 minutes ($p< 0.05$, $n= 57$) and 45 minutes ($p< 0.05$, $n=39$). This appeared to be consistent with the fall in V_{TE} after nursing suction (6.5.1).

6.5.4 Resistance

As with C_{rs}, age and weight are known to have significant between-subject effects on R_{rs} values. As can be seen from Figure 6-15, very high R_{rs} values were almost exclusively seen in children < 6 months or under 6 kgs. The greatest contribution to R_{rs} was most likely to be from the narrow tracheal tubes used in this population (3.1.3).

Figure 6-15: The influence of a) age and b) weight on R_{rs} values in the study population

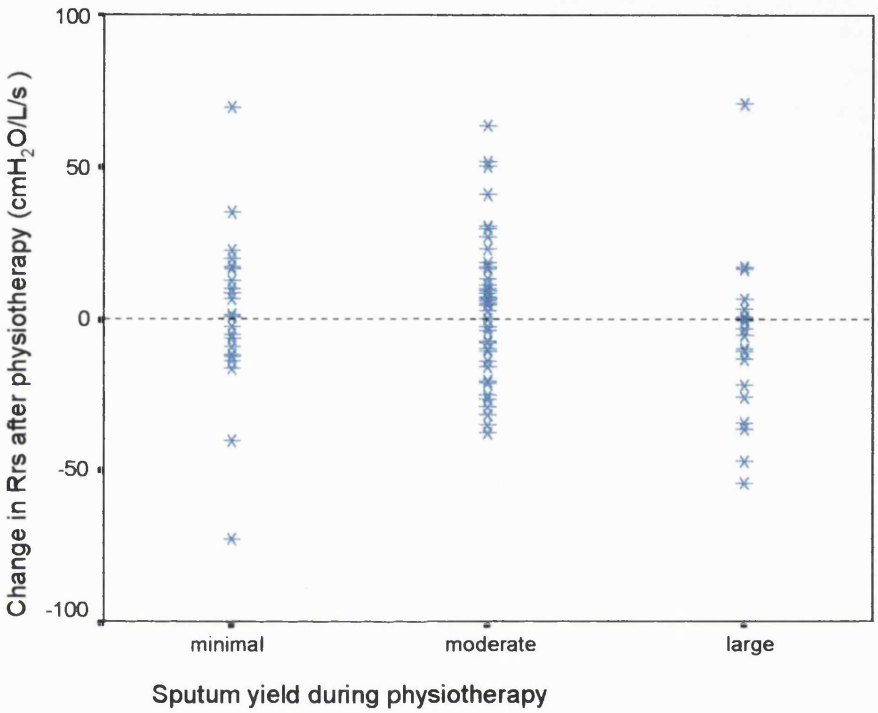


From Table 6-4, it can be seen that there was a tendency for R_{rs} to fall following physiotherapy after both 15 and 30 minutes. This trend only reached statistical significance ($p<0.05$) for infants on volume controlled ventilation but remained less significant ($p<0.09$) for those on pressure controlled ventilation.

This was supported to some extent by the association in this study between reported sputum yield and change in R_{rs}. Physiotherapists and nurses who performed the treatments were asked to score sputum yield as "minimal," "moderate" or "large", depending only upon their own subjective assessment of the amount of sputum retrieved during the treatment. The relationship between observed change in R_{rs} and the reported

sputum yield is shown in Figure 6-16, which shows that R_{rs} was more likely to be reduced after treatment in patients who had perceptibly large amounts of secretions removed during treatment.

Figure 6-16: Change in R_{rs} relative to reported sputum yield after physiotherapy



A sputum yield reported as 'large' after physiotherapy appeared to be associated with a greater reduction in R_{rs} than if sputum obtained was small or moderate.

There were no significant group changes in R_{rs} after nursing suction irrespective of ventilation mode. As discussed in 6.5.1, these results were confirmed using GLM analysis to exclude the influence of leak as a covariant.
Further non-parametric tests (Wilcoxon) were performed because of the large between-subject variability and skewed distribution of R_{rs} values. These tests confirmed the results.

6.5.5 CO_2 Values

The mean baseline $ETCO_2$ differed significantly ($p<0.05$) between the respiratory and cardiac population, with the mean being 5.9 kPa in the respiratory and 4.5 kPa in the cardiac population. This may have been related to the difference in mean age groups between populations and/or the difference in ventilation strategies used in each unit.

There were no significant group changes in VCO_2 or $ETCO_2$ as a result of either physiotherapy or nursing suction at any time interval after treatment (Table 6-4 and Table 6-5). This result remained consistent even when data were separated into groups according to ventilation mode or diagnosis and when GLM analysis was performed to examine the influence of leak.

There was a tendency for $PeCO_2$ to fall ($p<0.10$) immediately after physiotherapy and a statistically significant drop in $PeCO_2$ after 30 minutes ($p<0.05$, n=75). When GLM analysis was performed to exclude the influence of leaks, the tendency for $PeCO_2$ to fall after 15 minutes due to treatment alone reached statistical significance ($P<0.05$) which was sustained 30 minutes after physiotherapy. In addition, when analysis was split according to ventilation mode, the drop in $PeCO_2$ following physiotherapy was only significant in patients on pressure controlled ventilation.

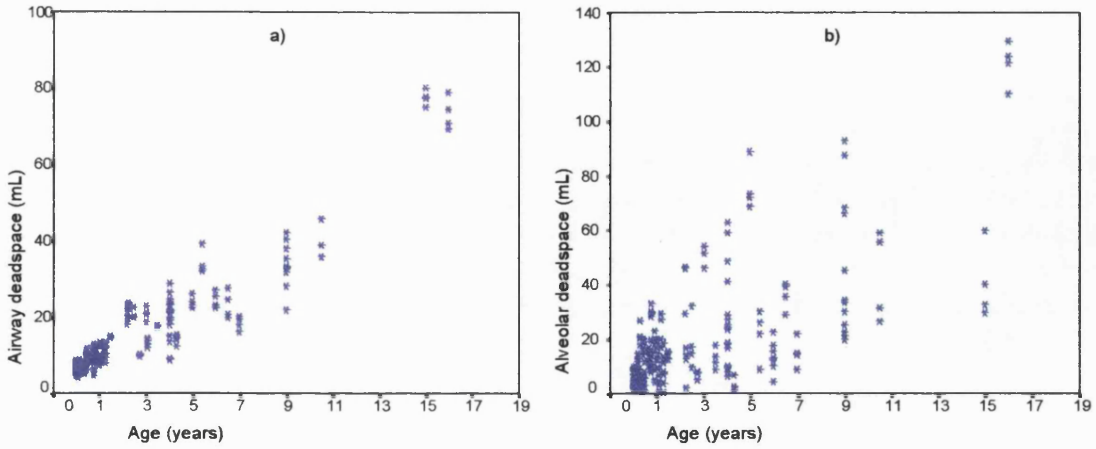
6.5.6 Deadspace calculations

From Table 6-4 and Table 6-5, it can be seen that there were statistically significant increases in $V_{D_{alv}}$ ($p < 0.001$) and $V_{D_{phys}}$ ($p<0.001$) following physiotherapy as well as a tendency for $V_{D_{phys}}/ V_T$ to increase. By contrast, there were no statistically significant changes in $V_{D_{airway}}$, $V_{D_{alv}}$, $V_{D_{phys}}/ V_T$ or $V_{D_{phys}}$ following nursing suction, irrespective of ventilation modality. Because of the large standard deviations present in $V_{D_{alv}}$, further non-parametric tests were performed which concurred with the standardised t-test.

Since the $V_{D_{airway}}$ component of $V_{D_{phys}}$ was unaffected by physiotherapy (Table 6-4), the observed changes in $V_{D_{phys}}$ must have been due to alterations in $V_{D_{alv}}$. Although statistically convincing, it is unclear whether this increase in deadspace constitutes a clinically significant change and potential mechanisms for these findings will be explored in section 7.2.4.

Age and weight were predictably important factors influencing $V_{D_{airway}}$, $V_{D_{alv}}$ and $V_{D_{phys}}$, with deadspace increasing with age (Figure 6-17). The increased spread of $V_{D_{alv}}$ (Figure 6-17 b) compared to $V_{D_{airway}}$ (Figure 6-17 a) is most likely related to the large variability in respiratory pathology in the study population, a factor which has less impact on $V_{D_{airway}}$.

Figure 6-17: The influence of age on a) $V_{D_{airway}}$ and b) $V_{D_{alv}}$



6.5.7 Arterial Blood Gases

All infants had arterial lines in situ and arterial blood gases were taken before and after physiotherapy and nursing suction. Baseline and post treatment values for pH were significantly higher in the cardiac population than in the respiratory group (7.44 vs 7.36 kPa). In addition, pH was significantly higher in children younger than 6 months (> 7.44) when compared to older age groups (pH < 7.40). The baseline $PaCO_2$ was lower in the cardiac group than the respiratory group (4.85 vs 5.85). Because of the lower mean age of the cardiac population, it is unclear whether between-subject influences were related primarily to age, ventilation strategies or diagnosis.

There was no significant group difference in pH or $PaCO_2$ or PaO_2 following either physiotherapy or nursing suction and no significant group changes in HCO_3-, base excess and O_2 saturation following nursing suction. These results remained consistent when groups were analysed separately according to diagnosis or age. There were however statistically significant reductions in HCO_3-, base excess and O_2 saturation following physiotherapy. These results were confirmed by non-parametric statistical tests (Wilcoxon) and remained consistent even when data were analysed separately according to ventilation mode. These results suggested that there was a mild metabolic acidosis following physiotherapy.

6.5.8 Differences between nursing and physiotherapy treatments.

To assess whether the effects of physiotherapy treatments were substantially different from those of nursing suction, mean changes after physiotherapy were compared with

those after nursing suction in the same patients using paired t-tests. Results from 82 patients who received both treatments on the same day are tabulated (Table 6-6).

Table 6-6: Comparing nursing suction with physiotherapy (paired data)

Parameter	*N*	*mean Δ post physio (P)*	*mean Δ post nursing (N)*	*95% CI (N-P)*	*p*
Tube leak (%)	83	-0.69 (3.65)	-0.81 (3.85)	-1.39 to 1.16	0.86
V_{TE}/kg (mL/kg)	83	0.11 (0.96)	-0.19 (1.26)	-0.66 to 0.06	0.10†
Rrs (cmH_2O/L/sec)	83	-7.69 (36.5)	-1.39 (15.4)	-2.41 to 15.0	0.15
Crs (mL/cmH_2O/kg)	83	0.01 (0.10)	-0.01 (0.08)	-0.05 to 0.00	0.09‡
VCO_2 (mL/min/kg)	83	0.01 (0.52)	0.05 (0.58)	-0.12 to 0.21	0.62
$ETCO_2$ (kPa)	83	-0.07 (0.64)	0.10 (0.50)	-0.01 to 0.34	0.07††
$PeCO_2$ (kPa)	83	-0.06 (0.35)	0.02 (0.29)	-0.02 to 0.17	0.14‡‡
$V_{D_{airway}}$/kg (mL/kg)	83	0.00 (0.16)	0.00 (0.14)	-0.06 to 0.05	0.84
$V_{D_{alv}}$/kg (mL/kg)	72*	0.29 (0.55)	-0.03 (0.57)	-0.12 to -0.51	**0.00**
$V_{D_{phys}}$/kg (mL/kg)	72*	0.29 (0.59)	-0.02 (0.60)	-0.10 to -0.51	**0.00**
$V_{D_{phys}}$/ V_T	72*	0.02 (0.14)	0.00 (0.14)	-0.01 to 0.00	0.26
pH	80*	-0.00 (0.06)	-0.00 (0.04)	-0.01 to 0.02	0.83
$PaCO_2$ (kPa)	80*	-0.08 (0.96)	0.03 (0.70)	-0.12 to 0.35	0.32
PaO_2 (kPa)	80*	-0.57 (3.66)	-0.59 (3.61)	-1.16 to 0.96	0.85
HCO_3- (mmol/L)	80*	-0.37 (1.50)	0.24 (1.80)	0.11 to 1.11	**0.02**
Base Excess	80*	-0.32 (1.56)	0.13 (1.83)	-0.09 to 0.97	0.10
O_2 Saturation (%)	80*	-0.77 (2.74)	0.13 (3.19)	-0.12 to 1.91	0.08

Results are expressed as mean (SD). Δ refers to 'change'. Significant results are in bold type. Of the 82 patients in whom paired data were collected for 15 minutes, recordings were continued for 30 minutes in 73 patients, 45 minutes in 27 patients and 60 minutes in 11 patients.

†:‡:‡‡$p<0.05$ after 30 minutes. ††p 0.09 after 30 minutes. All other parameters remained non-significant after longer time intervals.

**Data were dependent on blood gas analysis performed at discrete intervals immediately before treatments and 30 minutes afterwards.*

From Table 6-6, it can be seen that the effects of physiotherapy and nursing suction appear to differ in some respects. Certain parameters identified as being significantly affected by physiotherapy (Table 6-4), for example $V_{D_{phys}}$ and $V_{D_{alv}}$ were confirmed to be differently affected by physiotherapy and nursing suction treatments (Table 6-6). Changes in V_{TE} and C_{rs} did not emerge as significant following physiotherapy (Table 6-4), while there was a tendency for both to be reduced following nursing suction (Table 6-5). The difference between treatments for both V_{TE} and C_{rs} approached significance 15 minutes after treatment and reached significance after 30 minutes (Table 6-6). In addition, there was a tendency for $ETCO_2$ and $PeCO_2$ to increase after nursing suction but fall after physiotherapy which was apparent at both 15 and 30 minutes following treatment.

The decreases in HCO_3-, base excess and O_2 saturation noted after physiotherapy were either significantly different from the effects of nursing suction (HCO_3-), or approached significance (base excess and O_2 saturation) after 30 minutes. The tendency for R_{rs} to fall following both treatments was also evident, though less marked following nursing suction (Table 6-6).

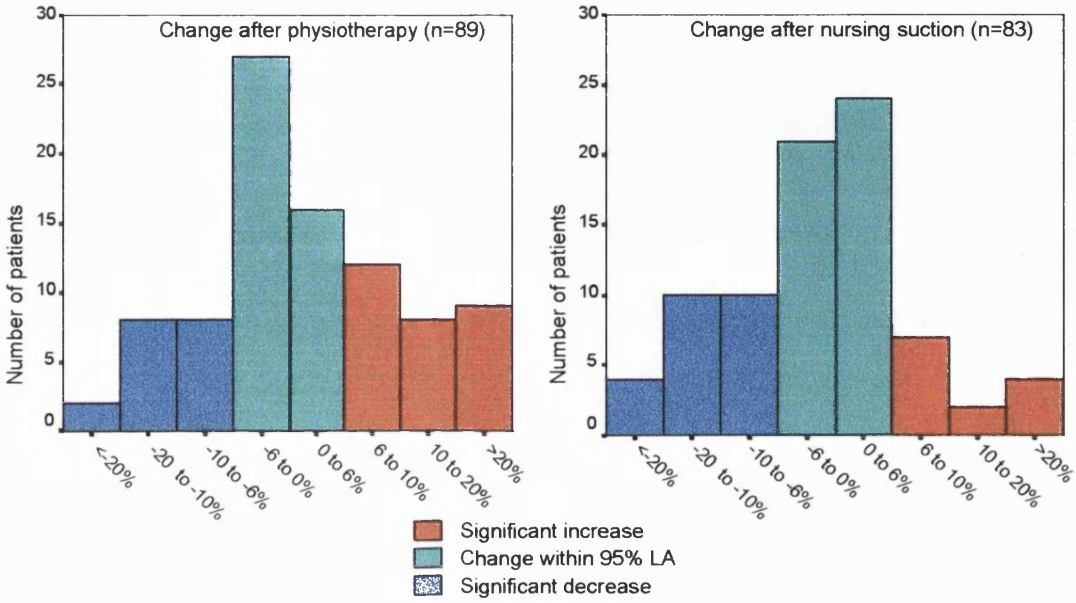
6.6 Individual results

Although it was important to assess whether there were statistically significant group differences between the effects of physiotherapy and those of nursing suction, it was also clinically relevant to assess the proportion of individuals in whom changes in respiratory parameters exceeded those expected in the absence of any clinical interventions. Since potentially clinically significant changes occurred amongst such individuals, attempts could be made to distinguish factors responsible for successful or unsuccessful treatments.

While there was little evidence for group changes in many respiratory parameters, there was considerable individual variation in response to treatment. In section 5.2.2.2, the relative change in respiratory parameters in the absence of any therapeutic interventions had been determined (Table 5-2). Within-subject changes in any parameter were defined as significant if they were beyond the 95% LA for normal variability. Figure 6-18 to Figure 6-25 indicate numbers of patients studied who demonstrated significant changes following physiotherapy or nursing suction.

6.6.1 Tidal volume

Figure 6-18: Significant individual changes in V_{TE} following treatment.

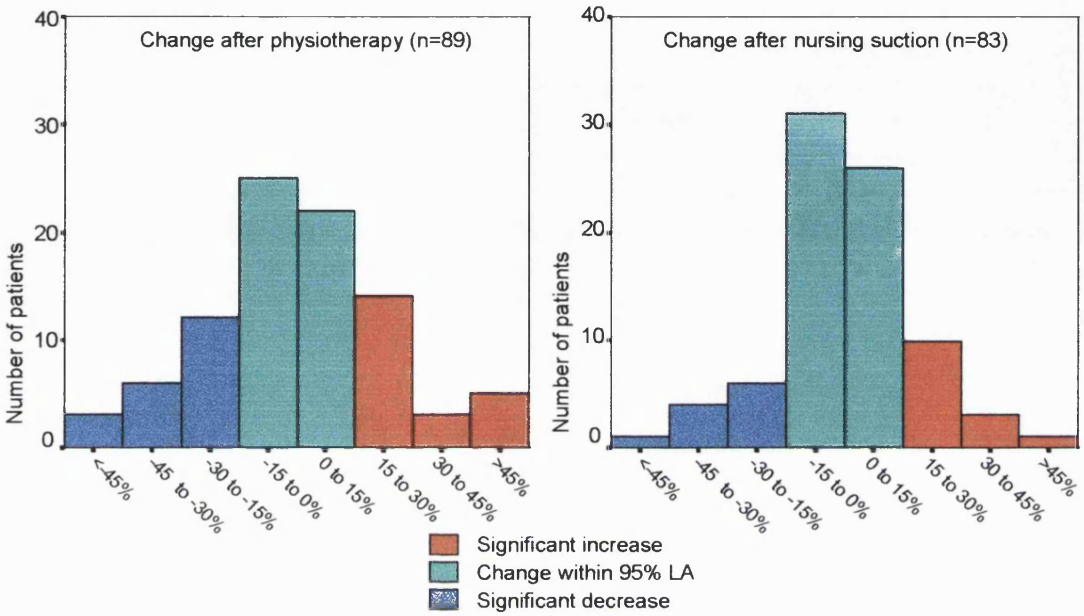


From Figure 6-18, 34% (30/89) of children studied demonstrated a significant increase in V_{TE} after physiotherapy while V_{TE} fell significantly in 20% (18/89). Following nursing suction, V_{TE} increased significantly in 16% (13/83) of patients studied while 29% (24/83) showed a significant fall in V_{TE}. These proportions were similar in patients for whom data collection continued for 30 and 45 minutes after treatment.

Attempts were made to identify factors which might predict improvement or deterioration. Multivariate analysis (ANOVA) was performed by grouping patients into 3 categories (significant increase, change within 95% LA and significant decrease) and then exploring the influence of factors such as age, diagnosis, ventilation mode or length of treatment performed. No factors emerged as significantly influencing the categories selected. However factors such as disease severity and oxygenation index were not assessed.

6.6.2 Resistance

Figure 6-19: Significant individual changes in R_{rs} after treatment

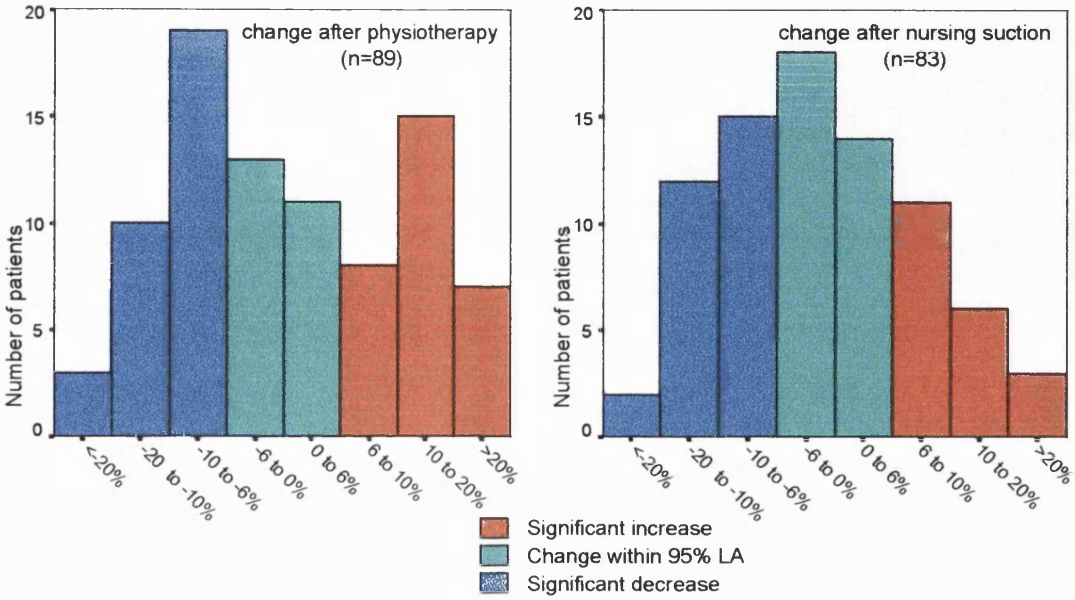


From Figure 6-19, it can be seen that 22% (20/89) of patients showed a significant reduction in R_{rs} after physiotherapy while the same number showed an increase. Following nursing suction, only 12% (10/83) demonstrated significant improvement, while 16% (13/83) showed an increase in R_{rs}. In both treatment groups, changes in R_{rs} were within 95% LA of normal variability for R_{rs} (within ± 20% change) in the majority of patients.

Once again ANOVA was performed to identify factors which might predict successful or unsuccessful treatments, but none were detected.

6.6.3 Compliance

Figure 6-20: Significant individual changes in C_{rs} after treatment

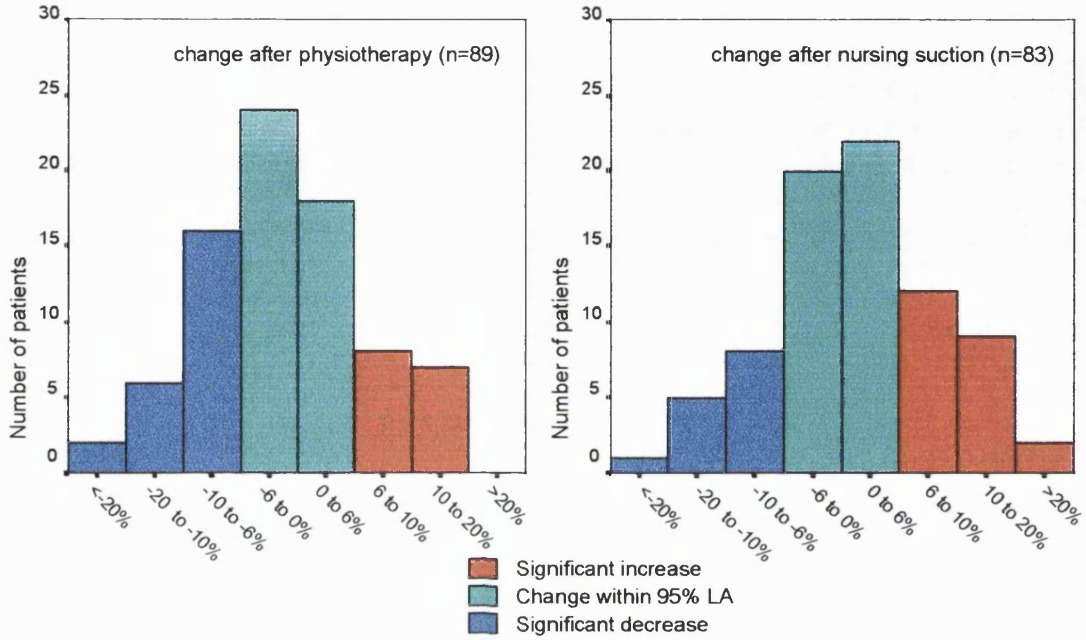


Although there were no significant group changes in C_{rs} after physiotherapy or nursing suction, there was a tendency for C_{rs} to fall after nursing suction in patients on pressure controlled ventilation (6.5.3). This tendency is masked in Figure 6-20, by inclusion of all patients. 34% (30/89) of patients showed significant improvement in C_{rs} after physiotherapy compared with 26% (22/83) after nursing suction. By contrast, approximately 34% showed significant reduction in C_{rs} after both treatments.

One neonatal cardiac surgery patient demonstrated a fall in compliance >20% after both physiotherapy and nursing suction. Three other individuals also demonstrated a >10% drop in compliance as a result of both physiotherapy and nursing suction (one cardiac surgery patient, one with Duchenne's muscular dystrophy and one after gastric transposition). A 9 year old girl with asthma demonstrated marked improvements (>30%) following both physiotherapy and nursing suction. On two occasions patients displayed improvement (>10%) with physiotherapy but deteriorated (>10%) with nursing suction and on two occasions, individuals improved (>10%) with nursing suction but deteriorated (>10%) with physiotherapy.

6.6.4 CO_2 values

Figure 6-21: Significant individual changes in $PeCO_2$ after treatment



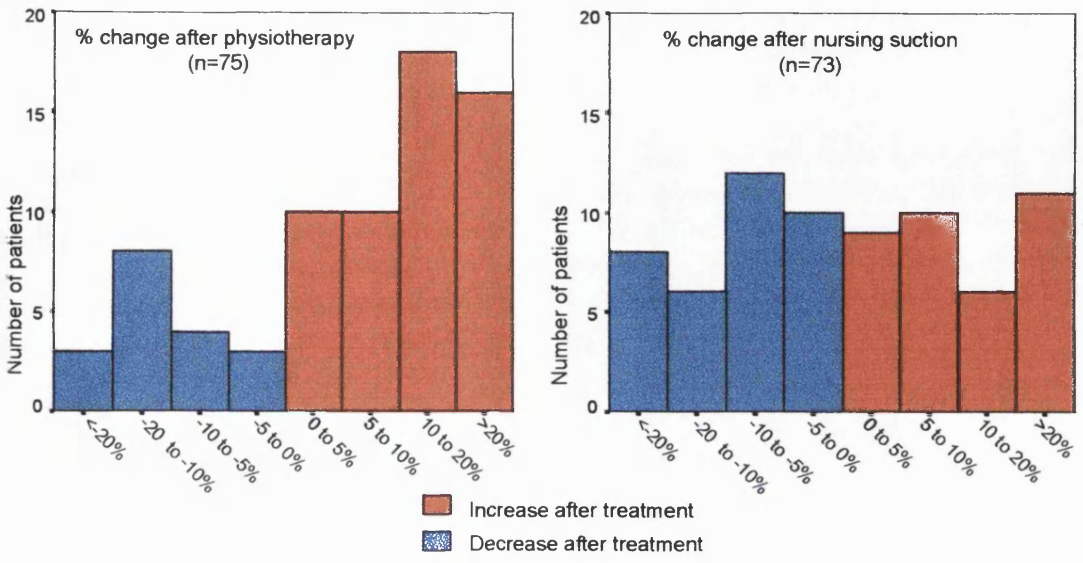
From Figure 6-21, it can be seen that 27% (24/89) of patients showed a significant reduction in $PeCO_2$ after physiotherapy compared with 17% (14/83) after nursing suction. Following physiotherapy, 15% (13/89) showed a significant increase in $PeCO_2$, while 28% (23/83) showed a significant increase following nursing suction. Similar changes after both physiotherapy and nursing suction were observed for $ETCO_2$.

In addition, 26% (23/89) of subjects showed a clinically significant increase in VCO_2/kg following physiotherapy while 29% (26/89) showed a decrease. Following nursing suction 23/83 (28%) and 20/83 (24%) showed an increase or reduction in VCO_2/kg respectively. Five individuals showed a significant increase in VCO_2/kg of more than 20% in response to physiotherapy and 5 showed a decrease of similar magnitude.

6.6.5 Deadspace calculations

No data were available on the variability of deadspace parameters in the absence of interventions, hence it was difficult to assess the level at which changes could be considered significant. However, the relative change in individual values of $V_{D_{phys}}$ following physiotherapy is summarised in Figure 6-22.

Figure 6-22: Relative changes in $V_{D_{phys}}$



The statistically significant increase in $V_{D_{phys}}$ ($p < 0.001$) following physiotherapy (Table 6-4) is clearly illustrated in Figure 6-22, where 75% (56/75) of patients showed an increase in $V_{D_{phys}}$ following treatment and over 45% (36/75) had an increase in $V_{D_{phys}}$ greater than 10%. By contrast only half (36/73) the patients showed an increase in $V_{D_{phys}}$ following nursing suction. Similar figures were obtained for $V_{D_{alv}}$ data. There was no statistically significant group changes in $V_{D_{airway}}$ following physiotherapy or nursing suction and no significant individual differences were detected.

6.6.6 Arterial Blood Gases

There were no significant group differences in pH, $PaCO_2$ or PaO_2 following either physiotherapy or nursing suction. Normal variability of blood gases was not assessed in this study, making it difficult to estimate the magnitude of change that would suggest clinical significance. Sasse et al. found that the spontaneous variability of $PaCO_2$ in 28 adult patients was considerable (CV: 4.7%) (Sasse et al. 1994). Since no published data describing normal variability of blood gases in paediatric patients were available, these data were used to investigate magnitude of changes in the current study population. In this study 45% and 53% of patients had a change in $PaCO_2$ following physiotherapy and nursing suction respectively that exceeded normal variability (CV>4.7%). Following physiotherapy and nursing suction, 21% and 25% of patients respectively, had changes in $PaCO_2$ which represented twice the normal variability (CV>10%). Only 5% and 7% of patients had a change in $PaCO_2$ with CV>15%. Approximately equal numbers of patients had an increase in $PaCO_2$ as had a decrease, after both physiotherapy and nursing suction.

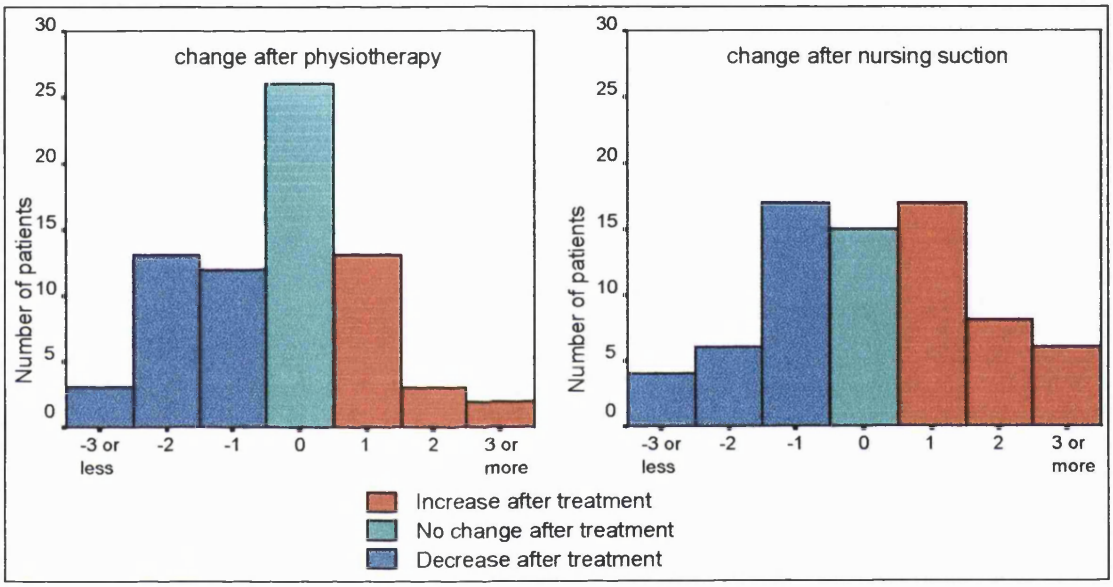
Variability of PaO_2 has also been found to be considerable (CV: 6.1%) (Sasse et al. 1994). In the current study, 61% and 58% of patients had changes in PaO_2 which exceeded normal variability (>6%) after physiotherapy and nursing suction respectively. Changes in PaO_2 greater than 12% were experienced by 28% and 29% of patients after physiotherapy and nursing suction respectively. Changes in PaO_2 greater than 18% were experienced by 18% and 15% of patients after physiotherapy and nursing suction respectively. Approximately 60% of patients in whom changes in PaO_2 exceeded normal variability, experienced a fall from baseline values after treatment, while the remainder improved. Approximately 70% of patients in whom a change in PaO_2 was more than double that of normal variability, experienced a fall from the baseline value after treatment, while the remainder improved. In patients who experienced a change in PaO_2 greater than 18%, 80% experienced a fall in baseline value after physiotherapy, while only 63% experienced a fall after nursing suction.

Sasse et al. found that the mean SD for pH was 0.012 in stable patients (Sasse et al. 1994). Following physiotherapy, 64% of patients had a change in pH with an SD in excess of 0.012. Of these, 65% experienced a fall in pH after physiotherapy treatment

while the remainder increased. Following nursing suction, 59% of patients had a change in pH with an SD in excess of 0.012 and of these, 57% experienced a fall in pH, while in the remainder pH increased.

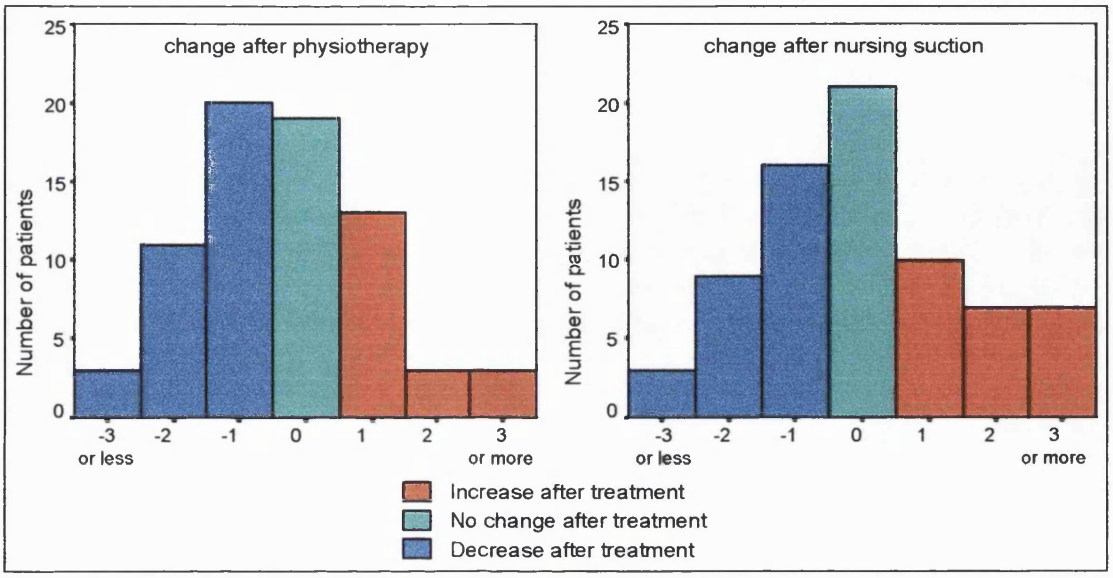
There were statistically significant reductions in HCO_3-, base excess and O_2 saturation following physiotherapy. Histograms below illustrate the proportions of individuals with changes of potential clinical significance.

Figure 6-23: Individual changes in HCO_3- after treatment



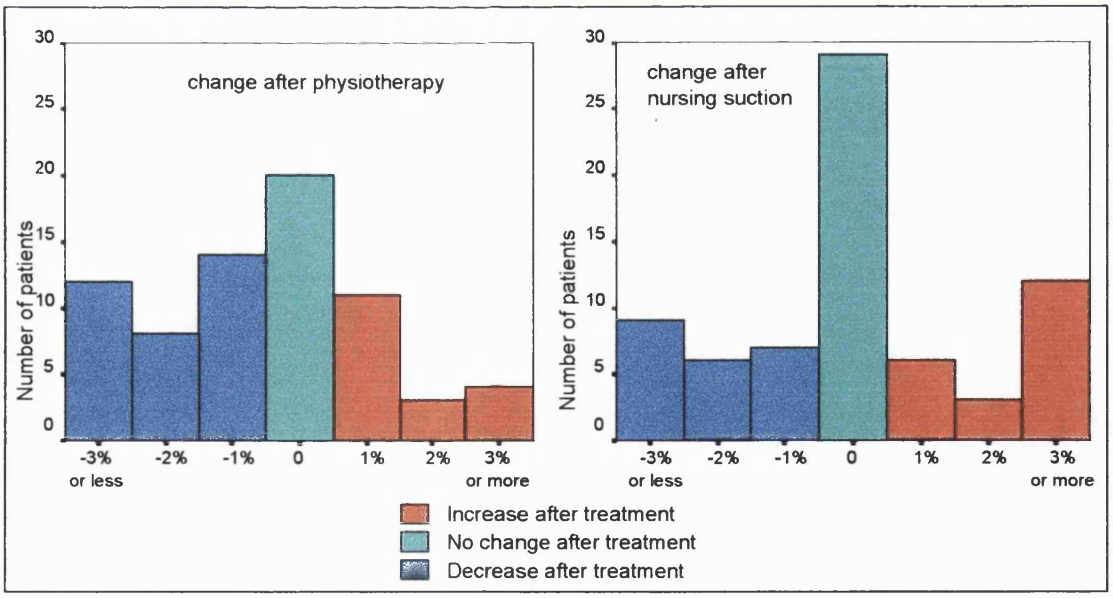
The greatest individual fall in HCO_3- was of 7 mmol/L after physiotherapy and the greatest individual gain was of the same amount after nursing suction. In general, however, apart from these 2 cases, individual gains or losses in HCO_3- after treatment did not exceed 3 mmol/L.

Figure 6-24: Individual changes in base excess after treatment



The biggest individual change in base excess was -5 after physiotherapy. From Figure 6-24, base excess tended to fall in the majority of patients after physiotherapy or nursing suction, although this only reached statistical significance in the physiotherapy group.

Figure 6-25: Individual changes in O_2 saturation



The largest individual change in O_2 saturation was a fall of 20% after nursing suction. From Figure 6-25, it was more likely for O_2 saturation to remain unchanged after nursing suction than after physiotherapy.

6.6.7 Individual patients' responses to physiotherapy

In addition to analysing group and individual responses to physiotherapy and nursing suction in terms of individual respiratory parameters, relative changes in parameters within individual patients were also investigated. Table 6-7 illustrates demographic data on individuals who showed significant within-subject changes in V_{TE}, C_{rs} or R_{rs}.

Table 6-7: Demographic data on individuals with significant changes in V_{TE}, C_{rs} or R_{rs}

*Patient***	*Age*	*Weight*	*Gender*	*Diagnosis / surgery*
1	13 months	7.7 kg	female	Gastric transposition
2	10 days	2.7 kg	male	Tracheal segment repair
3	9 years	25 kg	female	Asthma
4	3.5 months	4.3 kg	female	Cardiac surgery (AVSD)
5	5 months	6.9 kg	male	Cardiac surgery
6	13 years	22.4 kg	female	Heart-lung transplant
7	8 months	6.8 kg	male	Cardiac surgery (VSD)
8	3 months	4.0 kg	female	Haemangioma (neck)
9	5 months	5.6 kg	female	Cardiac surgery (AVSD)
10	4 weeks	3.1 kg	male	Cardiac surgery (Truncus A.)

*** Patient identification numbers in this table are related to patient numbers in Table 6-8 and Table 6-9 in which respiratory function data before and after physiotherapy are presented.*

From Table 6-8, it can be seen that improvements in V_{TE} were always accompanied by an increase in C_{rs}, a decrease in R_{rs}, and a decrease in $PaCO_2$. PaO_2 behaved less predictably, with some patients showing a decrease in PaO_2 following physiotherapy, despite apparent improvements in respiratory mechanics. This may have been related to an increase in metabolic demand or change in V/Q balance associated with the intervention. Values of $ETCO_2$, VCO_2 and $PeCO_2$ were also unpredictable following physiotherapy.

Table 6-8: Examples of individuals with clinically significant improvements after physiotherapy

*Patient***	*1*	*2*	*3*	*4*	*5*
Tube leak (%)	0.4%	-0.7%	-3.4%	-2.2%	-1.5%
	4.7→5.2	*10→9.3*	*4.4→1.0*	*15→13*	*3.4→1.9*
V_{TE}/kg (mL/kg)	87%	21%	17%	24%	23%
	4.9→9.2	*7.8→ 9.4*	*7.2→ 8.5*	*10 →13*	*5.2→ 6.4*
R_{rs} (cmH_2O/L/sec)	-38%	-29%	-54%	-26%	-21%
	51→32	*167 → 118*	*28 →13*	*124 → 91*	*73 → 58*
C_{rs} (mL/cmH_2O/kg)	100%	14%	51%	20%	31%
	0.4→0.8	*0.8→0.9*	*0.8 → 1.2*	*0.8 → 0.9*	*0.5 → 0.7*
VCO_2 (mL/min/kg)	21%	17%	-16%	10%	27%
	5.6 → 6.6	*4.8 → 5.6*	*5.1→ 4.3*	*3.3 → 3.6*	*3.5→4.4*
$ETCO_2$ (kPa)	-42%	-15%	-10%	-20%	12%
	10.0 → 6.0	*6.7→5.7*	*7.6→6.8*	*4.2→3.3*	*4.8→5.4*
$PeCO_2$ (kPa)	-36%	-4%	-17%	-13%	19%
	7.0 → 4.5	*3.2→3.1*	*4.2→3.5*	*2.4→2.1*	*2.3→2.8*
$V_{D_{airway}}$/kg (mL/kg)	16%	0%	45%	15%	1%
	1.1 → 1.2	*3.0→3.0*	*0.9→1.3*	*1.6→1.8*	*1.5→1.5*
$V_{D_{alv}}$/kg (mL/kg)	-72%	-3%	-6%	50%	7%
	0.4 → 0.1	*1.4→1.4*	*3.7→3.5*	*4.2→6.3*	*2.7→2.9*
$V_{D_{phys}}$/kg (mL/kg)	-16%	-1%	4%	41%	6%
	1.5 →1.3	*4.4 →4.4*	*4.6→4.8*	*5.8→8.1*	*4.2→4.4*
$V_{D_{phys}}$/ V_T	-50%	-19%	-33%	13%	0%
	0.3→0.2	*0.6→0.5*	*0.6→0.4*	*0.6→0.6*	*0.6→0.6*
pH	4%	1%	2%	0%	0%
	7.2 →7.4	*7.4→7.4*	*7.2→7.4*	*7.4→7.4*	*7.4 →7.5*
$PaCO_2$ (kPa)	-46%	-19%	-44%	-21%	-15%
	10 →5.6	*7.3→5.9*	*11.7→6.6*	*4.7→3.7*	*6.1→5.8*
PO_2 (kPa)	-24%	17%	3%	11%	-23%
	11→8.3	*10→12*	*12→13*	*11→13*	*12→9.5*
HCO_3- (mmol/L)	0%	-7%	-20%	-8%	-9%
	27→27	*30→28*	*35→28*	*24 - 22*	*22 - 20*
Base Excess	300%	-40%	-71%	0%	-20%
	-1→ 2	*5→3*	*7→2*	*2→2*	*-5→ -6*
O_2 saturation (%)	1%	-3%	3%	1%	1%
	91 - 92	*97 - 94*	*94 - 97*	*97 - 98*	*96 - 97*

*** Patient identification numbers are related to patient numbers in Table 6-7. Data are presented as **mean % change**, with magnitude of absolute change below.*

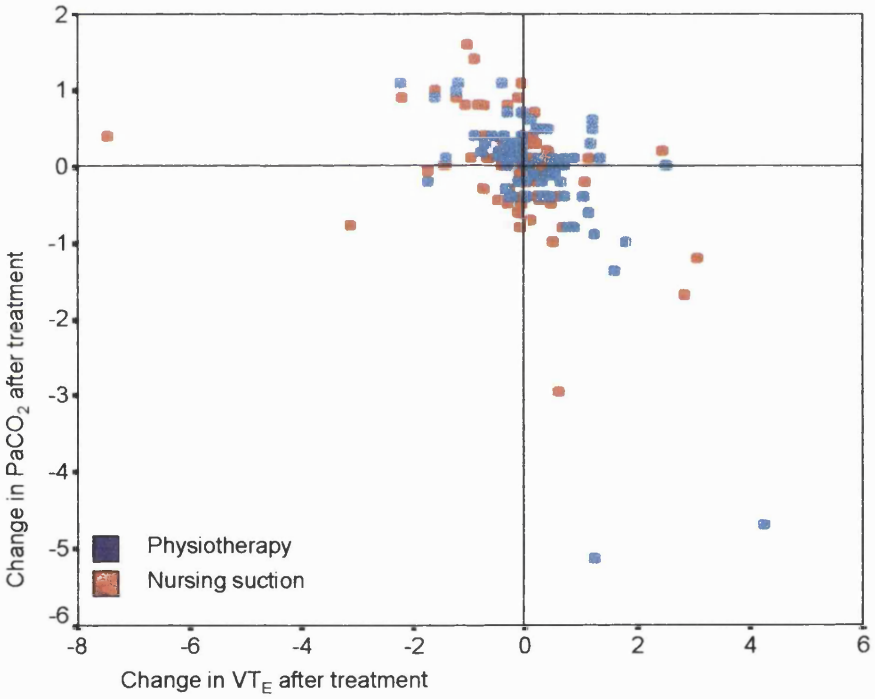
Table 6-9: Examples of patients with clinically significant deterioration following physiotherapy

** *Patient*	*6*	*7*	*8*	*9*	*10*
Tube leak (%)	-2.5%	-0.2%	2.3%	-4.3%	-2.5%
	6.1→3.6	*7.6→7.4*	*15→17*	*20→16*	*14→11*
V_{TE}/kg (mL/kg)	-16%	-16%	-13%	-38%	-18%
	13→11	*7.8→6.6*	*7.0→6.1*	*5.9→3.7*	*9.0→7.4*
R_{rs} (cmH_2O/L/sec)	71%	19%	18%	10%	7%
	24→42	*102→121*	*50→59*	*60→66*	*77→83*
C_{rs} (mL/cmH_2O/kg)	-39%	-20%	-14%	-6%	-20%
	1.2→0.7	*0.7→0.5*	*0.7→0.6*	*0.5→0.6*	*0.8→0.6*
VCO_2 mL/min/kg)	-41%	-26%	5%	-28%	-18%
	3.8→2.2	*2.5→1.9*	*3.1→3.2*	*4.0→2.9*	*4.6→3.8*
$ETCO_2$ (kPa)	12%	8%	-21%	36%	16%
	5.9→6.6	*3.9→4.2*	*3.0 →3.7*	*4.5→6.1*	*3.4→4.1*
$PeCO_2$ (kPa)	-31%	13%	19%	13%	11%
	2.1→1.4	*1.9→1.7*	*2.1→2.5*	*3.0→3.4*	*2.2→2.5*
$V_{D_{airway}}$/kg (mL/kg)	no abg	4%	3%	-14%	-23%
		1.4→1.4	*1.3→1.3*	*1.3→1.1*	*3.0→2.3*
$V_{D_{alv}}$/kg (mL/kg)		8%	-20%	208%	-33%
		3.1→3.4	*1.9→1.5*	*0.2→0.7*	*1.0 → 0.7*
$V_{D_{phys}}$/kg (mL/kg)		6%	-13%	21%	-26%
		4.5 →4.8	*3.2→2.8*	*1.5→1.8*	*4.0→3.0*
$V_{D_{phys}}$/ V_T		17%	-4%	26%	-2%
		0.6→0.7	*0.5→0.5*	*0.4→0.5*	*0.4→0.4*
pH		0.3%	0.3%	1.2%	1.3%
		7.4→7.4	*7.6→7.5*	*7.5→7.4*	*7.6→7.5*
$PaCO_2$ (kPa)		22%	10%	21%	23%
		4.5→5.5	*3.9→4.3*	*5.2→6.3*	*3.9→4.8*
PO_2 (kPa)		-25%	-14%	-53%	-14%
		15 → 11	*13→11*	*14→6.8*	*16→14*
HCO_{3^-} (mmol/L)		14%	4%	0%	0%
		22→25	*26→27*	*31→31*	*26→26*
Base Excess		300%	33%	-25%	-33%
		-3→0	*3→4*	*8→6*	*3→2*
O_2 saturation (%)		-2%	-2%	-13%	0%
		98→96	*99→97*	*99→86*	*99→99*

** *Patient identification numbers are related to patient numbers in Table 6-7. Data are presented as* ***mean % change****, with magnitude of absolute change below.*

From Table 6-9, it can be seen that deterioration in V_{TE} was always accompanied by a decrease in C_{rs}, an increase in R_{rs}, an increase in $PaCO_2$ and a reduction in PaO_2. Values of $ETCO_2$, VCO_2 and $PeCO_2$ were unpredictable following physiotherapy. To assess whether the relationship between change in V_{TE} and $PaCO_2$ was sufficiently predictable to allow them to be used interchangeably, Pearson's correlation coefficient was calculated ($r = -0.636$, $p<0.01$). Although the relationship was significant (Figure 6-26), it was not sufficiently sensitive to suggest that $PaCO_2$ and V_{TE} could be used interchangeably in the clinical environment.

Figure 6-26: Relationship between change in $PaCO_2$ and V_{TE} after treatment.



*Correlation is significant at the 0.01 level.

7. Discussion

The three principal hypotheses at the outset of this study proposed that: a) the "CO_2SMO Plus" would be a useful clinical tool for evaluating the clinical effects of therapeutic interventions, b) respiratory physiotherapy in the paediatric intensive care unit improves respiratory function and c) respiratory physiotherapy is more effective than nursing suction at removing secretions and thereby improving respiratory function. The results of the study and the extent to which they succeeded in proving or disproving these hypotheses will be discussed, particularly in relation to relevant published literature. In addition, the limitations of respiratory function measurements in ventilated children and general limitations of this study design will be explored. Finally, potential future directions for research in this field will be discussed together with clinical recommendations based on the evidence available from this and other current studies for the application of evidence based practice.

7.1 Is the "CO_2SMO Plus" a useful clinical tool for evaluating the effects of therapeutic interventions?

The execution of the study involved measurements of respiratory function in ventilated children using the relatively new "CO_2SMO Plus" device. Thus an essential aspect of this study involved validation of the device in terms of its accuracy in the ventilated paediatric population and evaluation of its clinical usefulness. To accomplish this, *in-vitro* validation procedures were planned and executed (section 3), as well as pilot and *in-vivo* studies (section 5) to ensure that the "CO_2SMO Plus" was an accurate and objective tool for measuring respiratory function in ventilated children. Since an *a priori* decision had to be made with regard to the number of parameters to be used as outcome variables, only 10 of the 104 available respiratory function parameters were selected as appropriate and evaluated in addition to a few reference parameters such as respiratory rate, PEEP and peak and mean airway pressure. Thus the usefulness of the "CO_2SMO Plus" can only be commented upon specifically in relation to the parameters evaluated in this study. Following pilot studies it was realised that evaluation of the "CO_2SMO Plus" in paralysed patients would be essential before its potential use in spontaneously breathing individuals could be considered.

Details of these tests and their results have been presented in sections 3 and 5.

7.1.1 Evaluation of methods and equipment

The manufacturer's specifications suggested that the accuracy and performance of the "CO_2SMO Plus" were acceptable for the nature of this research. However, further studies were undertaken to confirm these data because in the clinical environment, special considerations such as the addition of a tracheal tube have been known to cause significant degradation of the accurate linear range (Jackson et al. (b) 1995).

The volume integration of all sensors was found to be accurate and the addition of tracheal tubes of variable sizes did not perceptibly change the accuracy of volume measurements for any of them. The linear ranges of all sensors with and without tracheal tubes attached were accurate within broad and acceptable clinically encountered flow ranges. Pressure recordings were also found to be accurate for all sensors and assessment of pressure / flow relationships revealed that the R_{app} of the neonatal flow sensor contributed a relatively small amount to total R_{rs}, and that the R_{app} of the paediatric and adult flow sensors contributed negligibly towards total R_{rs}. The Least Squares Analysis algorithms employed by the "CO_2SMO Plus" software for calculation of R_{rs} and C_{rs} were cross checked against multiple linear regression of the raw data points of flow, pressure and volume and confirmed to be analogous. In addition, comparison of "CO_2SMO Plus" C_{rs} calculations against known C_{rs} values in a neonatal lung simulator revealed accuracy within a variety of physiological conditions. Finally, CO_2 measurements displayed by the "CO_2SMO Plus" were compared with known CO_2 concentrations and the percentage error was found to be <5% for all sensors. Deadspace measurements in the "CO_2SMO Plus" were validated (Wenzel et al. (b)1999; Wenzel et al. (c)1999) and validity of the i-Stat blood gas analyser were established by other authors and were not repeated in this study.

Early pilot and *in vivo* studies exposed concerns about the validity of C_{rs} and R_{rs} data obtained in partially ventilated or spontaneously ventilating individuals and clarified the duration of measurement required to obtain representative baseline data. In addition, normal variability for selected respiratory function parameters in muscle relaxed, fully ventilated patients was established so that significant changes could be identified and the

effect of sensor disconnection was investigated. Finally the effects of tracheal tube leak on measurements of respiratory function were thoroughly investigated so that limits of applicability for data obtained could be identified. Thus from validation work and *in vivo* studies undertaken at the beginning of this study, it appeared that the "CO_2SMO Plus" respiratory monitor was an accurate and potentially useful measurement tool in the paediatric intensive care unit.

It should be noted however that measurements in this study were undertaken in special and controlled circumstances on muscle relaxed and fully ventilated patients. Early measurements on spontaneously breathing patients generated data that were extremely variable and difficult to analyse. Validation of the "CO_2SMO Plus" under general intensive care unit conditions was not established, and applications for this equipment may be limited by other factors including the inability to distinguish between spontaneous and ventilator breaths in patients receiving assisted mechanical ventilation. The sophistication and sensitivity of breath triggering on modern ventilators may mean that pressure controlled breaths may be difficult to distinguish from pressure supported spontaneous breaths.

The "CO_2SMO Plus" equipment was relatively easy to use at the bedside and provided on-line real time information about pulmonary function. However, software available at the time of the study did not provide continuous calculated values of tracheal tube leak and to date the manufacturers continue to resist requests to adapt software to calculate and display this data continuously for clinicians at the bedside. Thus validity of C_{rs} and R_{rs} measurements could only be roughly estimated at the bedside by a crude judgement of leak magnitude derived from the discrepancy between V_{TI} and V_{TE} on the flow volume loops. It was only during detailed retrospective analysis of exported data that the validity of these outcomes could be confirmed. This would be of extremely limited value to clinicians at the bedside wishing to make instantaneous decisions on the basis of accurate C_{rs} or R_{rs} calculations.

Trend data generated from the average values of breath by breath data for each parameter have the potential to be genuinely useful in the intensive care unit, both by providing an instant and objective measure of efficacy of therapeutic interventions and

by providing an indication of spontaneous deterioration or improvement in respiratory function so that timely and appropriate changes in ventilator management could be instigated. Good examples of these benefits were encountered periodically in individuals throughout the course of the study while other monitoring methods, including arterial blood gas measurements (because of the intervals between sampling), were insensitive to these clinical changes. In addition, examination of flow, pressure and volume wave forms has the potential to assist in optimising ventilation rate as well as the ratio between inspiratory and expiratory time. The shapes of flow volume, pressure volume and $SBCO_2$ curves have the potential to provide immediate and diagnostic information about many aspects of respiratory function including C_{rs}, R_{rs}, air trapping or the presence of secretions in the large airways.

However, the expense of this type of monitoring is considerable and the benefits would be unlikely to apply in all cases. "Single patient use" flow sensors currently cost in excess of £31 and good graphics displays are possible only with a computer monitor incorporated into the measurement circuit. It is beyond the scope of this study to provide analysis of risks, benefits and health economics associated with the provision of routine respiratory function monitoring to all patients receiving mechanical ventilation. The decision as to whether this type of monitoring should be provided routinely or selectively in addition to standard monitoring is at this time unsupported by an evidence base. It is also difficult at present to anticipate selection criteria for monitoring, although critically ill, paralysed patients requiring ventilation for several days would seem to be more appropriate for example than those requiring brief ventilatory support following surgery.

7.1.1.1 Software problems with "CO_2SMO Plus"

The software developed by the "CO_2SMO Plus" manufacturers to manage respiratory function data is continually evolving to meet the requirements of intensive care monitoring in patients of all ages. The monitoring device had both hard and software problems initially and at the outset of this study, some relating specifically to equipment recently adapted for use in infants and some general software faults. Some of these were resolved slowly over time, but new versions of the software were constantly being

released, with parameters changing names and abbreviations, both mid project and between versions and systems. Some of these problems were identified only because of intensive and careful scrutiny of data and may not have been evident to medical staff at the bedside, unaware of the limitations of the software and equipment. The lack of thorough clinical validation of biomedical equipment prior to release remains a significant problem in incorporating new technology into the intensive care unit environment (Frey et al. (a) 2000; Frey et al. (b) 2000). Feedback from the manufacturers was intermittent, and often slow.

7.1.1.2 Phase delay

Any equipment which calculates or derives parameters from raw data signals depends on the fact that the signals are obtained simultaneously so that there is no phase delay in the processing of these signals which will lead to errors in calculation. In the "CO_2SMO Plus", for example, R_{rs} is calculated from raw pressure and flow signals and delays between these transducers (if they were connected in series) would lead to errors in R_{rs} calculation. Fletcher et al. found that even small phase shifts between flow and CO_2 signals could lead to significant errors in deadspace calculation (Fletcher and Jonson, 1984).

The compact sensor design of the "CO_2SMO Plus" overcomes these concerns by the fact that the infra-red CO_2 sensor straddles the pressure / flow sensor in the neonatal and paediatric models, thereby ensuring that flow, pressure and CO_2 are measured simultaneously. In the adult sensor, there is a 2cm difference between points of CO_2 and pressure/flow measurement. This would produce a negligible phase lag and degree of error in deadspace parameters calculated from these signals.

7.1.1.3 $PaCO_2$ and $PeCO_2$ calibration

Since the difference between $PaCO_2$ and $PeCO_2$ conveys potentially important information about the magnitude of deadspace, it would have been desirable to calibrate CO_2 measurements simultaneously between the "CO_2SMO Plus" and the i-Stat arterial blood gas analysers. However, this was not possible in practice since the i-Stat blood gas analysers and "CO_2SMO Plus" are both internally calibrated against known concentrations of CO_2. Both methods however showed minimal measurement error

when checked separately and thus although there might have been small errors in calibration between the instruments, these would not have substantially changed the magnitude or direction of clinical changes. In addition, these errors would have been negligible in comparison to the rounding errors discussed in section 5.2.3.

7.1.1.4 Early practical limitations of using the "CO_2SMO Plus" to monitor respiratory function in ventilated infants.

Several practical problems were encountered specifically in relation to the use of the "CO_2SMO Plus" in the clinical environment. Broader considerations with regard to the limitations of respiratory function measurements in ventilated patients will be discussed later in the chapter (7.4).

There were important and valid concerns with regard to the potential increase in dead space and the potential for CO_2 retention introduced by insertion of the flow sensor into the ventilator circuit, especially in critically ill preterm infants (Wenzel et al. (b)1999). The additional deadspace introduced by the neonatal flow sensor was <1mL and this was felt to be acceptable in full term neonates and infants. This concern was largely overcome by limiting recruitment of subjects to term babies or infants and children in this study. The added deadspace of the "CO_2SMO Plus" neonatal flow sensor is amongst the smallest available but the potential for CO_2 retention in preterm infants remains a concern in future studies involving this population group.

Prior to the development of the paediatric flow sensor, the "CO_2SMO Plus" manufacturer's guidelines suggested that all patients with an internal tracheal tube diameters of 4.0mm or more be measured with the *adult* flow sensor. The linear range of the adult flow sensor was however incapable of valid measurements under the low flow conditions sometimes encountered in small patients with a tracheal tube of 4.0mm diameter. In some of these patients volume could not be successfully integrated and rejection criteria for imperfect wave forms meant that there was inadequate data available for $SBCO_2$ or $ETCO_2$ to be calculated. This problem was overcome by using flow as an indicator for selecting appropriate sensor size rather than tracheal tube diameter and in some instances (prior to the development of the paediatric flow sensor), it was appropriate to use the neonatal flow sensor in patients with a tracheal tube

diameter of as much as 6.0mm. Since all patients were muscle relaxed and fully ventilated, concerns that the resistance created by adding the neonatal flow sensor to a large diameter tracheal tube would increase work of breathing. In addition, there was no evidence for CO_2 retention in any individual where the neonatal flow sensor was connected to a tracheal tube larger than 4.0 mm.

Early software limitations prohibited entry of body weight values of more than 9.9kg for the neonatal flow sensor and did not permit entry of body weight values to 2 decimal places. In these cases, weight corrected parameters such as V_T per kilogram were recalculated during analysis.

Excessive collection of water in the ventilator tubing was associated with poor performance of the infrared CO_2 sensor. Methods for connection and disconnection were modified to minimise moisture accumulation in the sensor and water was regularly emptied from ventilation tubing. Careful ventilator tubing placement and removal of excess moisture prior to measurements improved performance in later studies.

Early soft and hardware faults left the data collection system vulnerable to crashing. Data could not be automatically saved during measurements and because of this, critical data were lost on a number of occasions. Constant communication with the manufacturer's and feedback from them resulted in resolution of most of these problems.

7.1.1.5 Summary

Respiratory function monitoring in ventilated children may be advantageous from both a clinical as well as research perspective. As a research tool, the "CO_2SMO Plus" has been shown to produce reliable data under controlled conditions in certain patient groups and as a clinical tool, it has the benefit of providing immediate feedback on the effects of therapeutic interventions as well as on spontaneous trends in clinical progress. The data storage capacity and non-invasive nature of the monitoring are additional benefits in the research and clinical environments.

The continuous and simultaneous measurement or calculation of several respiratory parameters provide essential clues about the efficiency of respiratory function and gas exchange that would not be available from examination of isolated parameters alone. The relationship between VCO_2 and $ETCO_2$ for example, will provide evidence of gas exchange when an arterial line is not in place for determination of blood gases. A parallel relationship between $ETCO_2$ or $PeCO_2$ and $PaCO_2$, indicates a steady state balance wherein CO_2 elimination matches production. When the trends of VCO_2 and $ETCO_2$ do not run parallel in a critically ill child with one rising while the other falls, this may indicate that CO_2 elimination is less efficient, with a rise in $ETCO_2$ reflecting a build up of CO_2 in arterial blood. This might suggest the need for an increase in ventilatory support. By contrast, an acute fall in $ETCO_2$ coinciding with a rising VCO_2, may indicate an improvement in CO_2 elimination and ventilatory support might be reduced.

7.2 Does respiratory physiotherapy in the paediatric intensive care unit improve respiratory function ?

The second of the central hypotheses in the current study proposed that respiratory physiotherapy in the paediatric intensive care unit would improve respiratory function by increasing V_T and C_{rs}, decreasing R_{rs} and $V_{D_{phys}}$ and improving gas exchange. Statistically the results of the study did not support the proposals that V_T, C_{rs}, VCO_2, $ETCO_2$, pH, $PaCO_2$, PaO_2 or $V_{D_{phys}}$ improved immediately after physiotherapy. However, there was a significant small reduction in R_{rs} after physiotherapy in patients on volume pre-set ventilation and the same tendency ($p<0.09$) in patients receiving pressure pre-set ventilation. The unexpected and statistically significant, albeit small, increase in $V_{D_{alv}}$ and $V_{D_{phys}}$ after physiotherapy suggested that gas exchange and respiratory function may have deteriorated after treatment. In addition, there were statistically significant reductions in HCO_3-, base excess and O_2 saturation after treatment. The theoretical reasons and clinical implications of these results in context of comparisons with other published data are explored in detail below.

7.2.1 No significant change in V_T or C_{rs} after physiotherapy

There were no significant group changes in C_{rs} or V_T after physiotherapy but a tendency for both to decrease after nursing suction, which became statistically significant when effects of tracheal tube leak were adjusted for in analysis (6.5.2 and 6.5.3). Compliance is dependent upon and defined by the relationship between volume and pressure in the lungs. Thus a reduction in V_T after treatment would be expected to be accompanied by a reduction in C_{rs} as long as ventilator pressures remained unchanged. C_{rs} depends on numerous factors including tissue elasticity, lung water content, surfactant action, pulmonary blood flow and volume and the visco-elastic properties of the respiratory system. The separate elements of physiotherapy treatments, for example manual hyperinflation, saline instillation, chest wall vibrations might all have had different levels of influence upon any combination of these factors. The differences in C_{rs} response to physiotherapy and nursing suction were likely to be multi-factorial and related to differences in treatment techniques and how these influenced any combination of the factors mentioned above. In this study for example, C_{rs} response may have reflected differences in the way manual hyperinflation was performed. Jones et al. suggested that the hyperinflation aspect of physiotherapy treatment improved C_{rs} while the percussion aspect caused a deterioration (Jones et al. 1992). In this study, percussion was rarely performed during physiotherapy treatment, but manual hyperinflation was routinely performed before treatment, between cycles of treatment and following treatment before reconnection to the ventilator. Manual hyperinflation was less regularly performed during the shorter nursing suction events. On the other hand, negative suction pressure has been shown to be associated with collapse of alveoli and a reduction in C_{rs} (Velasquez and Farhi, 1964), and the tendency for V_T and C_{rs} to decrease following nursing suction may have been a reflection of a general technique in which suctioning (collapsing alveoli) played a greater role than manual hyperinflation (recruiting alveoli).

Previous studies in both adult and paediatric populations have produced conflicting evidence with regard to the effects of physiotherapy on V_T and C_{rs}, most likely due to heterogeneity of populations studied, interventions used and outcome measures reported. Some studies claimed an improvement in C_{rs} after physiotherapy (Winning et al. 1975; Mackenzie et al. 1980), while others suggested no change or a deterioration (Eales et al. 1995). It is particularly difficult to differentiate between studies in terms of

which aspects of treatment may have resulted either in improvement or deterioration of C_{rs}.

Tidal volume did not change after physiotherapy in this study. This concurs with a study on ventilated children conducted more than 20 years ago (Fox et al. 1978). Remarkably, V_T has rarely been used as an outcome in studies of physiotherapy efficacy in ventilated patients, but this may reflect the difficulty to date in measuring this parameter accurately (Brandstater and Muallem, 1969; Prendiville et al. 1986).
The available evidence suggests therefore that the effect of physiotherapy on C_{rs} may be variable and dependent on several factors, including the age of the patient as well as the duration of treatment and techniques performed. Factors such as diagnosis and severity of illness will very likely also be important in determining the response of C_{rs} to physiotherapy. Macnaughton found an association between improved compliance and recruitment of atelectatic lung (Macnaughton, 1997), probably due to an increase in V_T. Thus any physiotherapy treatment which succeeds in such recruitment might be expected to produce an improvement in C_{rs}. Atelectasis is currently well recognised as a criteria for selection of patients for treatment.

One study found that sedation and analgesia in ventilated children improved C_{rs} compared with awake patients (Irazuzta et al. 1993). Since all patients in the current study were paralysed and fully ventilated, the response of C_{rs} to physiotherapy may have been dampened. It is possible that the response of C_{rs} in awake and spontaneously breathing patients could be significantly greater.

7.2.2 Reduction in R_{rs} after physiotherapy

In this study R_{rs} decreased significantly 15 minutes after physiotherapy in patients on volume pre-set ventilation ($p<0.05$) and there was a tendency for the same result in patients with pressure pre-set ventilation ($p<0.09$), indicating that one of the primary goals of treatment (removing secretions) may have been achieved. These results were sustained and apparent 30 minutes after treatment. They may have been sustained for longer, but it was not possible to continue measurements in a large enough sample to assess this. There was no reduction in R_{rs} after nursing suction.

The literature regarding the effects of physiotherapy on R_{rs} is conflicting. Mackenzie et al. found no change in R_{rs} after physiotherapy in 42 ventilated adults (Mackenzie et al. 1980), while others found significant reductions in R_{rs} in paediatric populations after physiotherapy (Prendiville et al. 1986; Fox et al. 1978). Cochrane et al. found a significant reduction in airflow obstruction in non-intubated adults after chest physiotherapy (Cochrane et al. 1977). Because of the relative contribution of tracheal tube resistance to total R_{rs} in the ventilated patient, sensitivity of this parameter to therapeutic interventions may be dependent on, amongst other things, age, the length of the tracheal tube, position of or kinks in the tracheal tube and the relative size of the tracheal tube in relation to the tracheal diameter. The tracheal tube in paediatric patients is almost the same size as the trachea, and hence contributes a relatively small proportion of the overall R_{rs}. In adults however, the tracheal tube is only about half the width of the trachea and hence contributes substantially to overall R_{rs}. It is possible therefore that R_{rs} is a more sensitive measurement of respiratory function in ventilated children than in ventilated adult patients. However, because R_{rs} is proportional to the fourth power of the radius, small tracheal tubes generate a large resistance to flow and even small obstructions within an infant tracheal tube (for example due to secretions) will generate critical increases in R_{rs} by further reducing the effective lumen.

In any event, measures of airway resistance may be insensitive indicators of changes in *peripheral* airways, especially if homeostatic mechanisms for maintaining ventilation-perfusion relationships are effective (Menkes and Britt, 1980). Thus the changes observed in this study probably reflected removal of secretions from upper airways and are unlikely to have been associated with any changes in R_{rs} of peripheral airways. This was supported to some extent by the association in this study between reported sputum yield and change in R_{rs} (6.5.4).

Traditional methods of assessing the success of physiotherapy treatments, such as large sputum yield, can be remarkably deceptive and may not reflect the clinical status of the patient accurately. On a few occasions during the course of this study, patients with large sputum yield did not respond as expected with improved respiratory function but instead, exhibited a short term deterioration in V_T, C_{rs} or other respiratory parameters. This was possibly due to bronchial reactivity or other responses to the impact of

vigorous physiotherapy techniques. Individual physiological responses to physiotherapy may depend on many factors including the diagnosis, underlying respiratory pathophysiology, presence or absence of bronchial hyper-responsiveness and tracheomalacia. This raises doubts about whether sputum yield is an adequate or appropriate outcome criterion for physiotherapy treatment success, since although large sputum yield is intuitively beneficial for the patient, it is not always associated with a short term improvement in lung function. If it could be established that large sputum yield is associated with improved longer term outcomes (difficult in intensive care unit environments), then the immediate deterioration observed in some patients could be considered a reasonable risk which could be compensated for by a transient increase in ventilatory support. This assumption may not be reasonable in very ill children. On the other hand, while outcomes such as V_T or C_{rs} may reflect the short term clinical status of the patient, they may inaccurately represent the longer term benefit achieved by removal of secretions and may thus also be inadequately sensitive to the overall picture of treatment effect.

Oesophageal manometry was not performed in this study since in paralysed patients, it was not required for distinguishing between lung and chest wall compliance. In spontaneously breathing subjects however, the addition of oesophageal manometry could be helpful in studying the mechanical properties of the chest wall and lungs separately. The measurement of oesophageal pressure is a relatively invasive monitoring tool however, and may not always be accurate (Heaf et al. 1986).

7.2.3 Changes in CO_2 parameters and metabolic demand

In this study there were no significant changes in $ETCO_2$ or VCO_2 after physiotherapy, but $PeCO_2$ was reduced significantly ($p<0.05$) when effects of tracheal tube leak were adjusted for in analysis. The lack of change in VCO_2 after physiotherapy appears to contradict the findings of many previous studies, in which the haemodynamic and metabolic demands encountered during physiotherapy treatment created a significant rise in VCO_2 (Weissman et al. 1984; Singer et al. 1994; Horiuchi et al. 1997). However, this was most likely due to the fact that patients in this study were muscle relaxed and sedated during measurements, since these drugs have been demonstrated to reduce the

metabolic, haemodynamic, and ventilatory responses to chest physical therapy (Harding et al. 1993; Harding et al. 1994).

In contrast to the advantages of pharmacological paralysis in terms of reduced haemodynamic response to treatment, there are the disadvantages of artificially producing conditions in which patients have no effective means of sputum clearance (no cough, impaired mucociliary clearance, continuous mechanical ventilation) and in whom manual techniques of airway clearance become essential for reduction in morbidity associated with intubation and mechanical ventilation (King, 1987).

7.2.4 Significant increases in $V_{D_{alv}}$ and $V_{D_{phys}}$ after physiotherapy.

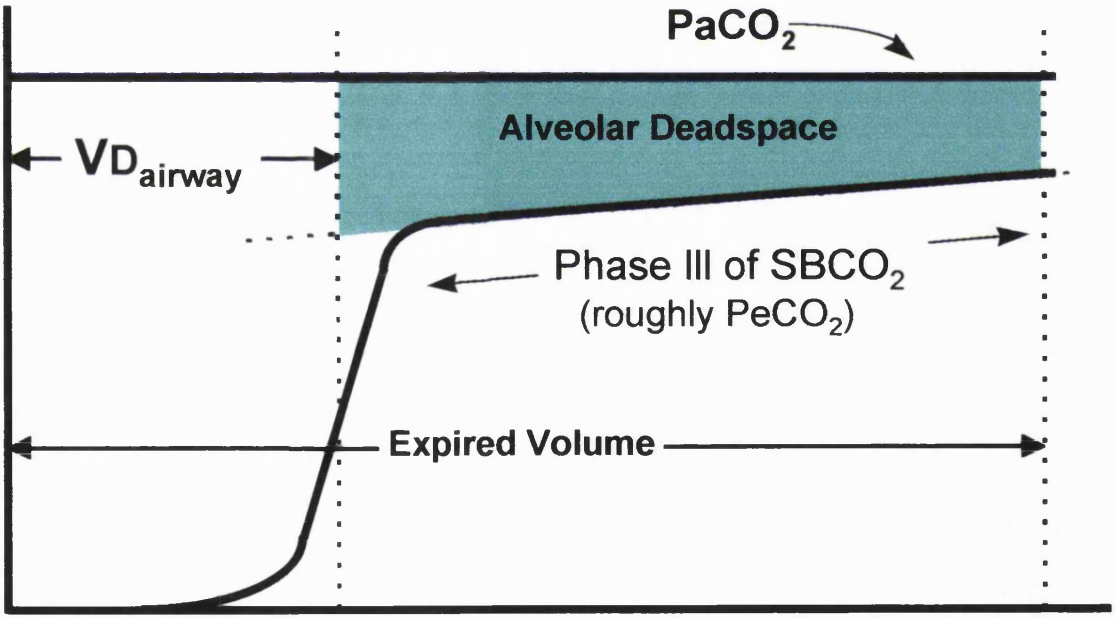
Unexpected findings from this study were the significant increases in $V_{D_{phys}}$ and $V_{D_{alv}}$ following physiotherapy which were not evident after nursing suction. Because $V_{D_{phys}}$ is comprised of $V_{D_{alv}}$ and $V_{D_{airway}}$, it is likely that this result reflects primarily the $V_{D_{alv}}$ component of $V_{D_{phys}}$, since $V_{D_{airway}}$ did not change after treatment. The increase in $V_{D_{alv}}$ implied some disruption in the pulmonary V/Q balance and sub-optimal gas exchange. However, although this disruption appeared to suggest that lung function was reduced 30 minutes after treatment, there were no other substantial indications (in terms of V_T, C_{rs}, R_{rs}, CO_2 parameters or blood gases) that respiratory function had been compromised by treatment. In fact, there was some suggestion that respiratory function might have improved slightly (reduced R_{rs}, decreased $PeCO_2$ with stable VCO_2).

Alterations in ventilation rate or tidal volume have not been found to have any effect on $V_{D_{airway}}$ (Fletcher and Jonson, 1984; Baker and Burki, 1987). Similarly, $V_{D_{phys}}$ was not influenced by increases in respiratory rate, but an increase in V_T significantly increased $V_{D_{phys}}$. These results indicate that V/Q matching could be influenced by a change in V_T . $V_{D_{airway}}$ has however, been shown to decrease in response to bronchial constriction (Olsson et al. 1999). In the current study, there were no significant group or individual changes in $V_{D_{airway}}$ after physiotherapy or nursing suction, indicating that bronchial constriction was unlikely to have been an important by-product of treatment in this patient population. Some physiotherapy techniques have been reported to cause bronchoconstriction (Campbell et al. 1975), and the lack of such effect in this study

might have been due to institutional differences in techniques, or the fact that all participants were sedated and muscle relaxed and thus less likely to respond in this fashion. It is therefore possible that $V_{D_{airway}}$ may be an important parameter in self ventilating patients or those with known underlying bronchial hyper-responsiveness.

There are several factors which could potentially have contributed to the observed increase in $V_{D_{alv}}$. $V_{D_{alv}}$ is determined by a complex and dynamic relationship between 3 factors graphically illustrated in Figure 7-1: $V_{D_{airway}}$, expired tidal volume (V_{TE}), and the gradient between $PaCO_2$ and P_ACO_2 (as reflected by $PeCO_2$: roughly phase III of the $SBCO_2$ plot).

Figure 7-1: Alveolar deadspace, defined by the area between $V_{D_{airway}}$, V_{TE} and the gradient between $PaCO_2$ and $PeCO_2$



The magnitude of $V_{D_{alv}}$ (shaded area) is determined by the complex dynamic relationship between the magnitude of $V_{D_{airway}}$, expired tidal volume and the gradient between $PaCO_2$ and $PeCO_2$.

Theoretically, good V/Q matching and optimal gas exchange would be reflected in a small gradient between $PaCO_2$ and $PeCO_2$. Any intervention which changes V/Q balance is likely to affect the gradient between $PaCO_2$ and phase III of the $SBCO_2$ plot, thereby changing the area ($V_{D_{alv}}$) enclosed by them (marked as A and B in Figure 7-2).

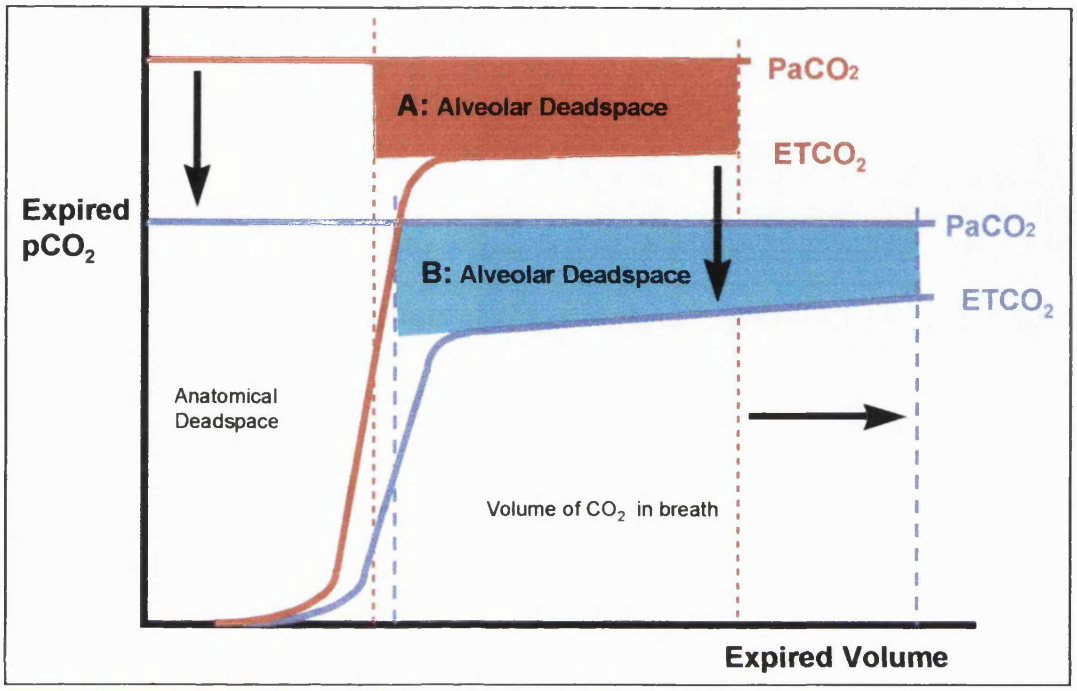
Interventions that move the V/Q ratio towards unity will decrease the gradient while interventions that disturb the balance will tend to increase the gradient.

The change in $V_{D_{airway}}$ after treatment was shown in this study to be negligible and thus unlikely to have contributed to the observed increase in $V_{D_{alv}}$. Thus changes in V_{TE} and the gradient between $PaCO_2$ and $PeCO_2$ were the primary variables influencing $V_{D_{alv}}$. An increase in the $PaCO_2/PeCO_2$ gradient accompanied by a decrease in V_{TE} might result in an increase or decrease in $V_{D_{alv}}$, depending of the magnitude of change in either V_{TE} and the $PaCO_2/PeCO_2$ gradient. Change in deadspace has not been associated with increased PaO_2 and the mechanism for change in $V_{D_{alv}}$ must therefore be related to other parameters (McGuire et al. 1997).

A case was reported in which an 11-month-old girl anaesthetised for surgery had atelectasis and a significantly elevated $V_{D_{alv}}$. After manual hyperventilation and tracheal suction the $V_{D_{alv}}$ fraction reverted towards normal values. The authors concluded from these observations, that atelectasis may be associated with more widespread disturbances of gas exchange than is generally realised, perhaps because of over-distension of adjacent lung regions (Fletcher and Larsson, 1985). In addition, the implication of this case report is that, as may seem intuitive, a reduction in $V_{D_{alv}}$ should be expected after resolution of atelectasis. However, this may not always be the case.

Figure 7-2 represents a theoretical scenario illustrating an increase in $V_{D_{alv}}$ after an apparently successful physiotherapy treatment. The $V_{D_{alv}}$ prior to treatment (area A) is defined by an elevated $PaCO_2$ and phase III slope, while the expired volume is relatively small. If after physiotherapy, the V_{TE}, $PaCO_2$ and phase III slope all respond as illustrated by the black arrows in Figure 7-2, the significant reductions in $PaCO_2$ and $PeCO_2$ as well as the increase in V_{TE} all indicate a successful treatment. However, because of the increase in V_{TE} and the relatively smaller changes in $PaCO_2$ and $PeCO_2$, the $V_{D_{alv}}$ (area B) after treatment is considerably bigger. Thus physiotherapy may produce an increase in $V_{D_{alv}}$ even when the outcome of treatment is considered successful.

Figure 7-2: $SBCO_2$ before and after physiotherapy



Area A represents V_{Dalv} prior to a successful physiotherapy treatment in which tidal volume is improved and $PaCO_2$ and $PeCO_2$ are reduced as illustrated by the black arrows. The V_{Dalv} following treatment (area B) is considerably bigger because of the increase in V_{TE} and the relatively smaller changes in $PaCO_2$ and $PeCO_2$. Thus physiotherapy may produce an increase in V_{Dalv} even when the outcome of treatment is considered successful.

Another consideration is the different response intervals of each of these factors after a significant intervention. The change in V_{TE} in response to treatment would be likely to be immediate whereas the change in gradient between $PaCO_2$ and $PeCO_2$ would depend on how quickly the V/Q balance could be re-established.

There is scant evidence in the literature to indicate exact timing for equilibrium between ventilation and perfusion, but available evidence points to the fact that there is a continuum of response times both in which hypoxic pulmonary vasoconstriction occurs and in which it is relieved. There is disagreement in the literature about the time required for hypoxic pulmonary vasoconstriction to reach its full intensity, although research suggests that the development of hypoxic pulmonary vasoconstriction is biphasic with an immediate phase followed by a delayed response which could take hours to develop (De Canniere et al. 1992; Leach et al. 1994; Zhang et al. 1995; Vejlstrup et al. 1997). The time taken for resolution of hypoxic pulmonary vasoconstriction would also depend on

many factors, including the proportion of lung involved (Barer, 1989), the age of the child, gravity and posture, how long the localised hypoxia (atelectasis) had been present (Beck et al. 1992; Marshall et al. 1994; Bialecki et al. 1998), mixed venous O_2 saturation (Domino et al. 1992), vascular distending pressure (Domino et al. 1993) and whether there was nitric oxide (NO) in the circuit or other pharmacological factors influencing the reactivity of pulmonary vasculature. NO has been shown to be capable of rapidly (within 30 minutes) reversing marked induced hypoxic pulmonary vasoconstriction (Roberts et al. 1993; Pison et al. 1993; Channick et al. 1994; Lonnqvist, 1997). In addition, pulmonary microvascular networks are extremely complex in nature and reactivity to hypoxia is perceptibly different in different lung regions (Oyamada et al. 1997). In a study by Taskar et al., minute ventilation was electively increased or decreased in 44 sedated and fully ventilated adults. After 20 minutes, $V_{D_{alv}}$ had decreased in patients who had minute ventilation reduced but remained unchanged when minute ventilation was increased (Taskar et al. 1995). This study demonstrates both the potential difference in time taken for development and resolution of V/Q mismatch as well as the seemingly incongruous reduction in $V_{D_{alv}}$ after a reduction in minute ventilation.

Most hypoxic pulmonary vasoconstriction studies explore gross lung pathology changes which are induced in laboratory settings rather than the more subtle and localised continuum of pathologies encountered in a clinical population, thus it is even more difficult to extrapolate information regarding the timing of V/Q rebalance. Given these variables in the clinical environment, it is virtually impossible to suggest the length of time required for pulmonary reperfusion of previously atelectatic areas recruited during physiotherapy. It is likely however that pulmonary perfusion to acutely acquired atelectasis would resolve relatively more quickly than that to chronic collapse, and that neonatal patients would respond more quickly than older patients, as would patients with NO or high inspired FiO_2. Older patients with chronic lobar collapse will be more likely to show a sluggish pulmonary reperfusion response to resolved atelectasis. It is probably reasonable to suggest that an interval of 30 minutes following physiotherapy (when blood gases in this study were taken and $V_{D_{phys}}$ calculated) might have been generally insufficient for V/Q equilibrium to be completely re-established.

If, as illustrated in Figure 7-2, physiotherapy improved alveolar ventilation, by recruiting atelectatic areas and removing secretions, whilst pulmonary perfusion had not had time to readjust, the result would be an increase in $V_{D_{alv}}$ as observed in this study. However, the increase in $V_{D_{alv}}$ could also be explained by a decrease in pulmonary perfusion, or a combination of increased ventilation and decreased perfusion. It is difficult to ascertain which of these was primarily responsible for the observed increase in $V_{D_{alv}}$. Other outcomes of the study were examined to assist with interpretation of this result.

There was no substantial evidence to suggest that pulmonary perfusion had been compromised after physiotherapy (Table 6-4), apart from the very small changes in derived arterial blood gas parameters (HCO_3-, base excess and O_2 saturation) which hinted at mild metabolic acidosis and which might have occurred as a result of reduced cardiac output. There were no changes in pH, $PaCO_2$ or PaO_2. Details of other variables such as pulmonary artery pressure, which might have provided further evidence for decreased pulmonary perfusion, were not recorded in this study since they were rarely monitored. A previous study found a significant decrease in intra-pulmonary shunt and no change in cardiac output after physiotherapy in 19 adults with post traumatic respiratory failure (Mackenzie and Shin, 1985), but the extent to which such findings can be extrapolated to the current study is limited.

Evidence for improved pulmonary ventilation in the current study was also scant but perhaps more persuasive. Changes in V_{TE} tended to be positive after physiotherapy, and the fact that $PeCO_2$ fell ($p<0.05$ after 30 minutes), while VCO_2 remained unchanged, supports this. The fall in $PeCO_2$ coupled with the fact that $PaCO_2$ did not change significantly after treatment would mean that $V_{D_{phys}}/ V_T$, calculated using the Bohr equation would be *increased* as would $V_{D_{phys}}$ and $V_{D_{alv}}$ in the absence of changes in $V_{D_{airway}}$. Confusingly, as suggested above, marked changes in V_T might also result in a *reduced* $V_{D_{alv}}$ after resolution of acute atelectasis (Fletcher and Larsson, 1985), but this would depend on rapid reperfusion and rapid equilibrium of V/Q matching. In addition, less successful treatments, (defined by an increase in the $PaCO_2/PeCO_2$ gradient and no change or deterioration in V_T) might also result in an enlarged $V_{D_{alv}}$. Therefore, it is

critical that the increase or decrease in deadspace is interpreted in the light of relative changes in other parameters.

A full understanding of the behaviour of $V_{D_{alv}}$ in response to therapeutic interventions would involve a study design that repeated blood gas measurements and deadspace calculations for several hours after treatment, until a new V/Q balance had been established in each individual. Therapeutic success would reflect ultimately that the V/Q matching established at the improved alveolar ventilation volumes had resulted in a smaller $V_{D_{alv}}$ and overall improvement in respiratory function. A study with this design would be very difficult to conduct in an intensive care unit environment, where clinical interventions or position changes which could confound both arterial blood gas values and tidal breathing parameters are regularly performed.

Since there is little evidence to substantiate either the argument for or against an increase in ventilation or a decrease in perfusion, it is possible that the combination of a small increase in ventilation and a small reduction in perfusion, was responsible for the significant increase in $V_{D_{alv}}$.

The increase in $V_{D_{alv}}$ 30 minutes after physiotherapy was of particular interest in this study because it represented a new and potentially sensitive measure of the impact of therapy on V/Q matching, a parameter which has not previously been explored in physiotherapy research because of the invasive nature of traditional ventilation/perfusion scanning.

Further investigation is required to assess full duration of this effect, and whether prophylactic measures should be taken to minimise the consequences of an increase in $V_{D_{alv}}$. Interestingly, any manoeuvres such as an increase in PIP, might take equally long to produce the desired effect given the potential delay in reversing hypoxic pulmonary vasoconstriction. In addition, $V_{D_{phys}}$ and $V_{D_{alv}}$ appear to be more sensitive to "hidden" physiological processes associated with physiotherapy treatments which are not particularly evident from examination of other parameters, and may be important in guiding treatments in the future. However, interpretation of deadspace changes is dependent on concurrent changes in more traditional outcomes (V_T, blood gases).

Without evaluation of simultaneous changes in other parameters, it would be difficult to assess whether $V_{D_{alv}}$ had increased as a result of a treatment which increased V_T, or a treatment which has increased the gap between $PeCO_2$ and $PaCO_2$. Thus $V_{D_{phys}}$ is not a particularly useful parameter when considered in isolation. While measurement of this parameter is not dependent on pharmacological paralysis, it is dependent on minimal tracheal tube leak, adequate t_E, an arterial line in situ for blood gas analysis, $ETCO_2$ monitoring and $PeCO_2$ calculation.

Nursing suction did not appear to have a significant effect on $V_{D_{alv}}$ or V/Q balance, which suggests a real difference in the physiological effects of both techniques. It is not clear however, whether these differences are a result of the manual techniques (most often chest wall vibrations) which distinguish the treatments, or simply a result of the fact that physiotherapy treatments are longer, involve slightly greater volumes of saline instillation and a slightly greater number of catheters (6.3).

Another factor which had the potential to influence measurements of deadspace was ventilation modality. There were no group changes in V_T after physiotherapy in either pressure or volume ventilated patients, but $V_{D_{alv}}$ increased significantly in both groups. The reduction in $PeCO_2$ was significant for the pressure controlled group, but not for the volume controlled group. In general, patients on volume preset ventilation would not have experienced gross changes in V_T after physiotherapy, although significant changes in distribution of alveolar ventilation may have occurred. A proportion of the delivered ventilation could for example be re-directed from hyperexpanded regions to previously atelectatic regions, recruited during treatment. These might have accounted for changes in gas exchange which occurred in the absence of changes in V_T. Thus, for patients on volume preset ventilation, the change in $V_{D_{alv}}$ is most likely to depend on the gradient between $PaCO_2$ and $PeCO_2$, unless there is a significant increase or decrease in $V_{D_{airway}}$. Successful treatments would therefore usually be associated with a decrease in the gradient between $PaCO_2$ and phase III, and a reduction in $V_{D_{alv}}$. In this study, there was a significant reduction in PIP 30 minutes after physiotherapy in the patients on volume preset ventilation which implies an improvement in C_{rs} in these patients, but further complicates interpretation of the increase in $V_{D_{alv}}$ in this patient group.

Children with cyanotic congenital heart disease have been shown to have significantly larger $V_{D_{phys}}/V_T$ than normal children or those with acyanotic heart disease ($p< 0.01$) (Mecikalski et al. 1984; Fletcher and Jogi, 1986; Bermudez and Lichtiger, 1987; Lindahl et al. 1987; Burrows, 1989). In addition, respiratory mechanics have been found to be abnormal in patients with cardiac disease both before and following cardiac surgery (Polese et al. 1999). While these factors may have contributed slightly to an increase in baseline values of $V_{D_{phys}}/ V_T$ in the cardiac surgery population, they would not have contributed to the observed changes after physiotherapy. This was confirmed both by the fact that nursing suction did not result in any change in $V_{D_{phys}}/ V_T$ and also by the fact that significant increases in $V_{D_{phys}}$ were demonstrated in the non-cardiac population after physiotherapy.

7.2.5 Changes in arterial blood gas values

The results of this study demonstrated no group changes in pH, $PaCO_2$ and PaO_2 after physiotherapy and small but statistically significant reductions in HCO_3-, base excess and O_2 saturation. The latter three parameters represent calculated values derived from the measured values of pH, $PaCO_2$ and PaO_2, none of which showed significant changes after treatment. HCO_3- is the most abundant buffer in blood plasma and represents the metabolic component of acid-base balance. The most plausible cause of reduction in HCO_3- would be from lactic acidosis (hypoxia). Base excess remains virtually constant during acute changes in $PaCO_2$ and reflects only the non-respiratory component of pH disturbances. SaO_2 is a useful predictor of how much O_2 is available for tissue perfusion. In general therefore the blood gas results suggest a mild metabolic acidosis that might be related to a decline in effective cardiac output or uncompensated increase in metabolic demand after treatment. These differences in HCO_3-, base excess and O_2 saturation were observed both for patients with primary cardiac diagnoses as well as non-cardiac paediatric intensive care unit admissions.

Changes in HCO_3-, base excess and O_2 saturation after physiotherapy have not previously been reported in the literature although several studies have reported an increase in metabolic demand as a result of physiotherapy and others have described

significant reduction in such metabolic demand with sedation or pharmacological paralysis (Hammon et al. 1992; Harding et al. 1994; Singer et al. 1994; Weissman et al. 1994; Cohen et al. 1996; Horiuchi et al. 1997). All patients in the current study were pharmacologically paralysed and would therefore have had significantly dampened responses to the stresses of physiotherapy treatment. It is thus interesting to note the extremely mild yet statistically significant demonstration of metabolic acidosis associated with physiotherapy in this patient group and important to realise the potential for significantly greater physiological responses in patients with less sedation or muscle relaxation.

The drop in O_2 saturation observed in the current study concurs with previous studies on the effects of suctioning (Simbruner et al. 1981; Kerem et al. 1990; Hussey, 1992). While several studies have reported a drop in PaO_2 after physiotherapy treatments or suction, this was not observed in the current study. This may have reflected the fact that the large majority of patients were pre-oxygenated prior to treatment via ventilator delivered or manual inflation breaths. There is strong evidence to suggest that pre-oxygenation, sedation and competence are mandatory to avoid hypoxaemia from suction (Stiller, 2000). The same review by Stiller, investigating the effects of physiotherapy on ventilated adults found that there was moderate evidence for improvements in arterial blood gases after treatment. This was not confirmed by the current study. The differences in mean baseline values of $PaCO_2$ and pH between patients on PICU and CICU may have reflected both the age group differences in each population, as well as the accompanying ventilation policies (a tendency to aim for more alkalotic gases in younger groups with cardiac diagnoses).

The fact that pH, $PaCO_2$ and PaO_2 did not change substantially with physiotherapy may reflect powerful physiological compensatory mechanisms optimising perfusion to match ventilation. Blood gases have been shown to be minimally disturbed until the whole system fails (Hillier et al. 1997; Stromberg and Gustafsson, 2000).

7.2.6 Monitoring respiratory function during treatment

At present, routine monitoring of respiratory function during physiotherapy treatment remains unfeasible. The "CO_2SMO Plus" or equivalent respiratory monitor would be an

impractical and inaccessible tool for measuring outcome after physiotherapy or nursing suction in all cases. The initial costs of monitors and laptop computers and the ongoing expenses of flow sensors and maintenance of such equipment would be prohibitively expensive for any physiotherapy department and impossible to justify in terms of costs recouped by avoiding unnecessary or harmful treatments. If however, such monitoring became commonplace in paediatric intensive care units and monitors were routinely set up at each bedside, the additional information about changes in pressure, volume, or CO_2 parameters would be very useful for physiotherapists seeking immediate and direct feedback about the efficacy of treatment. The need for and efficacy of tracheobronchial suction and lavage could be determined by monitoring the resistance of the respiratory system during mechanical ventilation (Prendiville et al. 1986).

7.2.7 Within-subject responses to treatment

Individual responses to physiotherapy were variable in this study with some patients demonstrating improvements in V_{TE}, C_{rs} and R_{rs} (Table 6-8) while others deteriorated (Table 6-9). These observations may be of more clinical relevance than statistical analysis of group changes and could potentially direct future research towards assessment of clinically significant within-subject changes.

While a reasonable number of individuals showed a statistically significant improvement in V_{TE} (30%), C_{rs} (37%) and R_{rs} (23%) after physiotherapy, an equal number showed a deterioration and still more did not have any change at all. Although the changes were significant when compared to the normal variability of these parameters in untreated patients, it remains unclear which proportion of these had *clinically* significant changes. The real numbers of patients appreciating clinically significant improvements will be somewhat less than the figures noted above. Following nursing suction procedures, only 11%, 26% and 15% showed a significant improvement in V_T, C_{rs} and R_{rs} respectively.

An optimistic interpretation of these results would focus on the fact that some patients improved significantly. A pessimistic interpretation would emphasise that the majority of patients treated showed either insubstantial changes after treatment or deteriorated which provides a strong argument for rationalising physiotherapy or nursing treatments

in the intensive care unit. Whichever interpretation is adopted, it is clear that more sensitive criteria for selecting patients who will respond favourably to treatment need to be established. It is equally important to establish criteria for recognising paediatric patients who will not benefit from treatment or who will be made worse by the intervention.

Individuals in the current study were coded according to whether they improved significantly, deteriorated significantly or showed no change in selected parameters. These codes were used to attempt to establish if there were any predictive factors for successful or unsuccessful treatments. Unfortunately, there appeared to be no predictable association between either improvement or deterioration after physiotherapy and age, diagnosis, ventilation mode or physiotherapy treatment details. It is possible that other factors such as severity of illness scores (oxygenation or ventilation indices) which were not prospectively recorded during this study may have been useful predictors. These should be included in further studies.

While physiotherapists in some intensive care units perform routine treatments in all patients with a view to preventing complications, others only treat when they believe there are specific patho-physiological reasons for doing so. It is not enough to suggest that routine treatments should be abandoned in favour of treatments based on sound clinical indications for physiotherapy or nursing suction, since all patients in this study were studied on the basis that after assessment they were deemed to require treatment. Traditional criteria such as auscultation, chest radiograph and increased ventilatory requirements were used to make these decisions. Since reliable criteria for treatment selection are difficult to establish, there might be an argument for delaying instigation of treatment until acute lobar atelectasis occurs. However, acute lobar collapse in critically ill children and small infants, may not be as well tolerated as in adults and may significantly delay recovery. It would thus be difficult to justify delaying treatment until a significant pulmonary problem occurred.

At Great Ormond Street hospital, ventilated patients are usually assessed for treatment at least once daily, and often, as part of these assessments, a very brief treatment is performed. It is the experience of the author and colleagues that, on occasion,

surprisingly large volumes of sputum have been suctioned from small infants in whom no clear indication (chest radiograph or auscultation) for treatment was evident. Although it is impossible to say with certainty that these patients would have run into trouble later on in the day, it must be assumed that their risk of lobar collapse or tube blockage would have been increased. In some cases plugs of secretions against the tracheal wall might not have generated the transmitted sounds generally associated with secretions in the upper airways. It would be senseless to perform 2-hourly treatments in the hope of avoiding complications, but there is perhaps some justification in performing a daily physiotherapy assessment/treatment in asymptomatic ventilated infants, to rule out the possibility of 'silent' secretions causing tube or airway obstruction. Tracheal tube blockage is an avoidable and unnecessary life-threatening event and since most ventilated infants have regular airway clearance procedures, it is difficult to establish how frequently tube obstruction is prevented by regular tracheal tube hygiene.

The evidence from this study is that physiotherapy and nursing suction treatments produce different physiological responses, and that the advantages conferred by physiotherapy treatment in terms of reducing R_{rs} may be of substantial benefit in certain patient groups. If quick, effective treatment prevents or reduces morbidity and mortality in a small number of patients, then perhaps 'over treatment' in some patients because of insensitive treatment selection criteria may be justified as long as doing so does no harm. The paediatric population is however, arguably more vulnerable than adults, and decisions regarding the value of any interventions should be undertaken with great caution.

7.2.8 Cross contamination between age, intensive care units, diagnosis and ventilation modality.

The observed differences in mean baselines values of pH and $PaCO_2$ between patients in the paediatric and cardiac intensive care units suggested essential differences between these populations which might have influenced responses to treatment. The cardiac intensive care unit population was younger and had predominantly pressure controlled ventilation while the respiratory population was older and had an even mixture of volume and pressure preset ventilation modalities. It was thus very difficult to distinguish between intensive care unit, diagnosis, age and ventilation mode in terms of

which variable primarily determined the response to treatment. In addition it was difficult to use any of these variables in ANOVA procedures because of the contamination of covariables. It remains unclear how this problem may be addressed in future except by separate analysis of the different patient groups.

7.2.9 Avoiding the harmful effects of physiotherapy

The potentially harmful haemodynamic, metabolic and respiratory effects of physiotherapy and suction treatments have been well described (1.2.2.7). Several authors have described methods for minimising or abolishing these effects and amongst these, adequate sedation, pre-oxygenation, and careful haemodynamic monitoring, are the most important. Further clear recommendations for evidence based practice include the necessity for careful monitoring of ICP and CPP when appropriate to ensure that there are no detrimental effects of physiotherapy treatment, as well as monitoring of airway pressure or tidal volumes when manual hyperinflation is used.

In the current study, there was no significant fall in PaO_2 after physiotherapy or nursing suction and this probably reflected the success of routine pre-oxygenation in avoiding this hazard. Given the large number of published reports on hypoxaemia following airway clearance techniques, this result supports the continued and routine practice of pre-oxygenation.

However, despite customary pre-oxygenation and careful haemodynamic monitoring in this muscle relaxed, fully ventilated population, there was still demonstrable and statistically significant evidence for mild metabolic acidosis following physiotherapy treatment. Since muscle relaxants, analgesia and sedation have all been shown to reduce the physiological demands associated with physiotherapy and tracheal tube suction significantly, it follows that the metabolic demands in a less sedated population would be likely to be substantially greater, and this should be borne in mind when planning any treatment in critically ill ventilated children. In view of the evidence that metabolic demands are increased during treatment (supported by the current study), an assessment of metabolic reserve should be made before intervening.

The potentially deleterious effects of physiotherapy should also be considered when planning appropriate timing of treatment. Popular practice involves timing physiotherapy treatments to coincide with nursing cares, to allow the child to 'rest properly' afterwards. It may in fact be more advantageous to ensure that treatment is not immediately preceded or followed by any significant clinical intervention unless absolutely necessary. There is no evidence to support the routine application in some units of hourly or even 2 hourly respiratory physiotherapy except in extremely unusual circumstances. It may even be of benefit to increase ventilatory support temporarily following treatment in critically ill patients in whom physiotherapy is clearly indicated.

The alleged connection between encephaloclastic porencephaly and chest physiotherapy in extremely preterm infants (Harding et al. 1998) was discussed in 1.2.2.7. Although none of the babies in the current study were preterm, the seriousness of this association should be considered, in light of the evidence that physiotherapy treatments are capable of producing significant physiological effects even in term babies and older children. Amongst the publications objecting to the conclusions reached by Harding (Beeby et al. 1998; Gray et al. 1999; Vincon, 1999), was a letter describing an alternative physiotherapy treatment for extremely preterm infants which the author claimed had been 'used for 25 years' (Vincon, 1999). Somewhat ironically, his alternative treatment is not evidence based and contains several seriously alarming features which calls into question the justification for physiotherapy treatments in this extremely vulnerable age group and exposes an urgent need for review of respiratory physiotherapy treatments in preterm babies. Vincon's forced expiratory manoeuvre adapted to the intubated preterm infant:

> *"is a manoeuvre that increases the expiratory time and recruits ejection volumes higher than those mobilised during spontaneous cough, which are very low in the preterm infant. This technique requires meticulous training and should be performed 3 times a day. No adverse effects have been noted except for desaturations, which can be compensated for with a transitory increase in inspired fraction of oxygen with close monitoring by pulse oximeter. In 1997, in 74 infants born between 24 and 27 weeks' gestation, we observed that 38% had intraventricular haemorrhage (Grade I to IV), and all cases of intraventricular haemorrhage were diagnosed before chest physiotherapy was initiated"* (Vincon, 1999).

Amongst the horrifying features of this description is the fact that Vincon appears to be proposing therapeutic collapse of airways which, in preterm infants, are very likely to be

surfactant depleted, and further, that he would continue such treatments in infants diagnosed with any severity of IVH. The cause of the observed desaturation is quite explicit. If this is the nature and quality of objections generated within the physiotherapy profession against publications such as Harding's, then it is not surprising that the practice of respiratory physiotherapy has been discontinued in many neonatal units.

7.2.10 Further research in paediatric physiotherapy

During 2000, two publications reviewed the evidence for physiotherapy treatments in intensive care, one of which focussed on ventilated children (Stiller, 2000; Krause and Hoehn, 2000). These reviews concluded similarly that there was an urgent need for further better designed studies. Stiller notes that virtually every aspect of physiotherapy management in ventilated patients needs validation (Stiller, 2000). A recent systematic review on chest physiotherapy for babies undergoing extubation from mechanical ventilation demonstrated that although treatment did not significantly reduce the rate of post extubation lobar collapse, there was a reduction in the rate of reintubation (Flenady and Gray, 2000).

A disturbing feature of many published physiotherapy studies is that the limitations of measuring respiratory function in ventilated patients experienced in this study (including tracheal tube leak) must have been encountered to a greater or lesser degree, yet these have rarely, if ever, been mentioned. There must be some degree of caution in interpretation of results from these studies since the validity of their findings is critically dependent on controlling or minimising these factors.

There is little or no evidence in the literature that physiotherapy prevents or is effective at treating common pulmonary complications in ventilated patients with the exception of acute lobar atelectasis (Stiller, 2000). The lack of evidence regarding the effects of physiotherapy does not necessarily mean that it is not good practice. It is likely, despite the lack of evidence, that the majority of intubated children require regular suction to maintain patent tracheal tubes and clear the central airways of secretions. The available evidence shows that physiotherapy may have short-lived beneficial effects in some children, although this in itself is not enough to suggest policies on treatment frequency.

There simply is not enough information to weigh benefits against the risks of treatment and costs associated with the provision of routine physiotherapy to children in intensive care who are receiving mechanical ventilation. The current study involved the measurement of multi-modality treatments rather than the effects of specific techniques, and there is little guidance for which specific individual treatment techniques offer advantages over others. Positioning has been shown to be of short term benefit for some patients (ARDS and unilateral lung disease) and there is some guidance for treatment of acute lobar atelectasis, but beyond that there is no evidence to support selection of some techniques over others for specific pulmonary conditions (Stiller, 2000). Thus the necessity for physiotherapy treatments in ventilated infants cannot be supported or refuted on the basis of available evidence.

A randomised controlled trial involving physiotherapy and nursing suction vs nursing suction alone could shed light upon whether physiotherapy treatments reduced the incidence of atelectasis or airway obstruction in ventilated individuals. Large subject numbers would need to be recruited and there would be some debate regarding the ethical issues of withdrawing established treatments. Studies demonstrating the efficacy of physiotherapy ideally need to be seen to contribute to the 'big picture' in terms of reduced ventilation time, reduced morbidity and mortality or reduced hospital stay. However, physiotherapy treatments are only likely to benefit a small proportion of patients significantly, and then only in the short term (Stiller, 2000). Since physiotherapy is only one of many interventions in a multitude of diagnostic and clinical scenarios, it would be extremely difficult to achieve the statistical power to prove either efficacy in terms of major outcomes (such as intensive care unit days) or cost effectiveness in terms of any subtle advantages of physiotherapy treatment in ventilated children.

Although this may cast a pessimistic shadow upon the ability of physiotherapy to achieve any credibility in studies of major outcomes, there remain basic and established facts of care requirements in artificially ventilated individuals:

1. airway clearance is compromised, especially in sedated or muscle relaxed patients,
2. the effects of anaesthetic significantly reduce respiratory function and

3. airway secretions must be removed so that complications associated with artificial ventilation are avoided.

It is thus at least intuitively clear that some degree of airway clearance procedures are essential in ventilated children. What remains to be clarified are issues such as the relative benefit of some techniques over others, the frequency of treatment required and the selection criteria for maximum benefit.

Thus although it is important to recognise the need for physiotherapy studies to enter the arena of multicentre blinded randomised controlled trials eventually, it is not feasible to do so until an understanding of short term effects of physiotherapy treatments in specific patient groups can be achieved. Reasonable assumptions can then be made about the likelihood of these effects influencing the longer term outcomes.

7.3 Is respiratory physiotherapy more effective than nursing suction at removing secretions and improving respiratory function in ventilated children?

The final hypothesis of this study aimed to establish whether respiratory physiotherapy treatments offered a significant advantage over routine airway clearance techniques used by nursing staff in ventilated children. To accomplish this, the effects of physiotherapy treatments and nursing suction on respiratory function were independently established. Then statistical tests were performed on the mean differences between physiotherapy and nursing suction effects within individuals in whom data had been collected for both techniques. Examination of treatment details revealed that physiotherapy treatments were generally longer, involved instillation of more saline and the use of more suction catheters per treatment. The results of the study suggested that there were differences in physiological effects between treatment techniques and these will be discussed below.

7.3.1 Changes in V_T and C_{rs}

While there were no significant changes in V_T or C_{rs} after physiotherapy, there was a tendency for both to fall 15 minutes after nursing suction ($p<0.08$), which was sustained and reached statistical significance ($p<0.05$) both at 30 and 45 minutes after treatment. The direction of change in C_{rs} and V_T after physiotherapy was positive (albeit

insignificant) whereas the direction of change after nursing suction was negative. Thus a comparison of the mean differences between techniques yielded a tendency ($p<0.10$) after 15 minutes for a difference between treatment modalities in terms of V_T and C_{rs} which reached significance after 30 minutes ($p<0.05$).

After physiotherapy 30% and 37% of all individuals showed a significant improvement in V_T and C_{rs}, respectively, while the remainder showed no change, or deterioration in these parameters after treatment. By contrast, following suction alone, only 11% and 26% of all individuals showed improvements in V_T and C_{rs} respectively with the remainder showing no change, or deterioration in these parameters. For both V_T and C_{rs}, there were more than twice as many patients with improvements in excess of 10% in the physiotherapy group than in the suction group. From these data, there is a suggestion that physiotherapy treatment may offer some advantage over nursing suction, if not in significantly improving V_T and C_{rs}, then at least in terms of not substantially worsening these parameters after treatment.

It is unclear why the treatments performed by physiotherapists did not have the same deleterious consequences for V_T or C_{rs} as suction alone. Perhaps, as suggested in 7.2.1, some aspects of treatment which distinguished physiotherapy from nursing suction, for example, manual hyperinflation or chest wall vibrations, somehow compensated for the detrimental effects of suction alone on V_T and C_{rs}. These adverse effects might be minimised by a policy of concluding each suction procedure with a few manual hyperinflation breaths to counteract any atelectatic effects of suction. Manual hyperinflation may have a short lived beneficial effect on respiratory function, but it has also been shown to cause adverse cardiovascular effects in some patients. Reducing the time of maximal inflation may improve the margin of safety in these patients (Rothen et al. 1999).

7.3.2 Changes in R_{rs}

There was a significant group fall in respiratory R_{rs} after physiotherapy but no significant group change in R_{rs} after nursing suction alone. Both treatment techniques had a common direction of change in that R_{rs} tended to be reduced. Thus comparison between

techniques did not yield a statistically significant difference ($p<0.15$), although physiotherapy treatment resulted in a substantially greater mean reduction in R_{rs} than suction alone.

7.3.3 Change in $V_{D_{phys}}$ and $V_{D_{alv}}$

The statistically significant increases in $V_{D_{phys}}$ and $V_{D_{alv}}$ observed after physiotherapy were discussed in detail in 7.2.4. These differences were not observed after suction alone and examination of paired data revealed that in respect of $V_{D_{alv}}$ and $V_{D_{phys}}$, this was a statistically significant physiological difference between physiotherapy and nursing treatment effect. The positive aspect of this result is that nursing suction appears not to have substantial effects on the balance between ventilation and perfusion in the lungs, which is desirable if suction is considered primarily as a maintenance procedure. On the other hand, suction alone is also less likely to be responsible for ultimately improving gas exchange and an improvement in the V/Q ratio.

7.3.4 Changes in blood gases

The small but statistically significant falls in HCO_3-, base excess and O_2 saturation observed following physiotherapy, were not seen after nursing suction alone. Comparison of the mean differences between groups demonstrated that the differences in HCO_3- were statistically significant while the differences in base excess and O_2 saturation approached significance ($p<0.10$). These data suggest that the slight increase in metabolic demand created by the more vigorous physiotherapy treatment is not apparent after nursing suction alone. Differences between physiotherapy and nursing suction in terms of pH, $PaCO_2$ and PaO_2 were not statistically significant.

7.3.5 Summary

The evidence from this study suggests that respiratory physiotherapy is different to nursing suction in several respects and that both may have important and complementary roles in the management of ventilated children. This study suggested that, when compared to nursing suction, physiotherapy:

1) is potentially more efficient at removing pulmonary secretions (decreased R_{rs})

2) is less detrimental in terms of C_{rs} and V_{TE}
3) causes significantly greater increases in $V_{D_{alv}}$ and $V_{D_{phys}}$
4) results in a reduced $PeCO_2$
5) causes mild metabolic acidosis as reflected by deterioration in HCO_3-, base excess and SaO_2.

The apparent physiological cost (albeit small and short lived) of physiotherapy treatment suggested by deterioration in arterial blood gas parameters and increase in deadspace volumes, may support the current policy of limiting physiotherapy treatments to patients exhibiting specific clinical indications.

Suction alone was associated with a slight tendency for C_{rs} and V_T to decrease and no other significant deterioration in respiratory function. Suction therefore remains an important, relatively benign method of maintaining the patency of the airway, without compromising critically ill ventilated children.

There is limited or conflicting literature regarding the physiological effects of separate manual components of physiotherapy treatments such as percussion or vibrations. The differences noted in this study between physiotherapy and nursing suction indicate that chest wall vibrations and positioning (either in terms of the techniques themselves or in terms of the additional time performing them) may confer additional physiological effects to the treatment which may have contributed to the observed differences in R_{rs}, $V_{D_{phys}}$ and $V_{D_{alv}}$.

A recent review of respiratory physiotherapy in ventilated adults found little or no evidence that routine physiotherapy in addition to nursing care prevents common pulmonary complications or is effective in altering the clinical course of pulmonary conditions commonly encountered in the intensive care unit (Stiller, 2000). Stiller also noted the lack of research comparing the ability of various professional groups to perform selected tasks, and the inability to suggest guidelines in terms of whom would be best suited to perform intensive care unit airway clearance techniques. The current study focused essentially on comparison between the effects of different treatment packages rather than relative abilities between professional groups. It has confirmed the

advantages and disadvantages of the more vigorous physiotherapy treatments as well as demonstrated the effects of suction procedures without manual techniques. It has not, nor was it intended to, suggest that one professional group is superior to another in terms of airway management in the intensive care unit.

It has also not managed to prove conclusively the hypothesis that physiotherapy is more effective than nursing suction in improving respiratory function in ventilated children. The first portion of the hypothesis (more effective at removing secretions) may be supported by the relatively larger reduction of R_{rs} following physiotherapy treatment, although the clinical significance of the results remains unclear. The latter portion of the hypothesis (improvement in respiratory function) has not been supported by the results of this study, but neither has the corollary. The debate regarding the relative advantages of physiotherapy versus nursing suction techniques is unresolved, primarily because the changes induced by either technique on the selected parameters were generally small and there was considerable heterogeneity in response.

The basic necessity of airway clearance procedures in ventilated children and the different advantages and disadvantages offered by physiotherapy and nursing suction, suggest that both techniques have important roles to play. The current and evolved practice in our intensive care unit is that regular suction by nurses is intermittently and less frequently supplemented by physiotherapy treatments in ventilated infants. This might offer the best of both techniques in that frequent, less physiologically intensive suction procedures keep the airway patent, while physiotherapy is performed less frequently but has the potential to be more effective at clearing secretions.

Another important aspect of the differences between physiotherapy and nursing suction is the essentially different philosophy regarding purpose of treatment. In general, nurses view tracheal tube suction as being a necessary routine, which maintains patency of the airway for ventilation and prevents accumulation of secretions. Physiotherapists at this hospital, on the other hand, believe that treatment should be based on careful assessment of clinical need in individual patients and claim that routine treatments are rarely performed. The aim of treatment is thus more proactive: to reverse adverse changes in respiratory status that are related to retention of secretions. When considered from this

perspective, the minimal group changes in respiratory function after nursing suction do not reflect failure in techniques, but success in maintaining airway patency with minimal physiological debt. The relatively greater physiological consequences of physiotherapy treatment should be accompanied by policies of selective treatment in which the benefits are considered to outweigh the risks of treatment.

7.4 Limitations of respiratory function measurements and study design in ventilated children

The intensive care unit is not a particularly easy research environment. Several factors contribute to problems with measurement in ventilated children and it remains difficult to control the multiple variables inherent in the management of these patients. Medical and nursing interventions are constantly and necessarily performed which may confound or influence measurements of physiological response to treatments. The continuous infusion of essential drug therapies such as diuretics may also interact with outcomes of interest and represent factors which are very difficult to control during research measurements. It is thus virtually impossible to acquire reliable data assessing the effect of singular therapies in ventilated patients unless the outcomes of interest are relatively immediate.

The impact of certain issues upon the success of this study were difficult to anticipate prior to commencement but will direct the design of future studies. Other difficulties were not easy to control within a paediatric intensive care unit environment and will continue to be a problem in future studies. The perceived limitations of the current study are discussed below

7.4.1 Physiological lung models

Most techniques for measuring respiratory mechanics are based on a linear single compartment model, in which the lung is represented as a balloon on a pipe (2.2). This model has two components, the compliance of the balloon and the resistance of the pipe. In the presence of a tracheal tube or any significant airway disease, such a simple model can rarely represent the respiratory system (Sly et al. 1996). In addition measurements obtained are difficult to interpret or compare because validity of the techniques have not been established in infants with normal lungs versus those with lung disease. It is

therefore with some caution that measurements in the intensive care unit should be interpreted.

In addition, deadspace measurements based upon the Bohr equation make the assumption that $PaCO_2$ is equivalent to P_ACO_2. In diseased lungs, where the alveolar arterial barrier may be compromised, this assumption is not valid. The assumption made by Enghoff ($P_ACO_2 \approx PaCO_2$) is less robust in critically ill children where pulmonary oedema or factors such as V/Q imbalance may inhibit the equilibrium between the PCO_2 in arterial blood and alveolar gas. The result of this mismatch in $PaCO_2$ and P_ACO_2 would be an over-estimation of V_D/V_T.

7.4.2 Mode of ventilation

The two main modes of ventilation used in paediatric patients are 'pressure preset' and 'volume preset' modes. While there is some evidence that the mode of ventilation will not significantly influence measurements of respiratory mechanics (Kessler et al. 2001), changes in other outcomes such as V_T and PIP are critically dependent on mode of ventilation and such data from patients on different modes of ventilation cannot be pooled for analysis, especially in studies which seek to evaluate the effects of therapeutic interventions. Responses to therapeutic respiratory manoeuvres such as physiotherapy will be different depending on whether volume or pressure preset ventilation prevails and the selection of outcome variables would have to reflect this. The numbers of subjects available for recruitment into respiratory function studies of therapy in ventilated patients is limited by this factor.

7.4.3 Changes in respiratory rate and volumes

Measurements of respiratory mechanics change when ventilatory rate or tidal volumes are changed. In general, an increase in respiratory rate would result in a decrease in both R_{rs} and C_{rs} (Nicolai et al. 1993). Thus measured changes in respiratory mechanics due to therapy could be invalidated by changes in ventilator rate during measurement periods. Similarly, the respiratory system is less compliant at high and low volumes. Consequently altering the level of PEEP, PIP or expiratory time, all of which can move

the infant to a different part of the pressure volume curve, can have a dramatic influence on the measured C_{rs}. R_{rs} may also be changed by differences in airway calibre and lung tissue resistance when delivered tidal volumes or flow are changed (Sly et al. 1996). It therefore becomes very difficult to interpret changes during serial measurements in an intubated ventilated subject, if there are changes in clinical condition and/or therapeutic interventions. The ideal research environment in the intensive care unit would thus require constant ventilation settings, but this is not always possible or desirable in sick ventilated infants. Every reasonable effort was made to minimise these known sources of error by avoiding ventilator changes during data collection periods in the current study and data were excluded when such adjustments were unavoidable.

7.4.4 Measurements of R_{rs} and influence of the tracheal tube

Respiratory system resistance is dominated by the upper airways and in ventilated patients, the tracheal tube creates a high resistance, turbulent flow and bypasses the upper part of the respiratory system which is usually important in maintaining dynamic control of lung volumes. The tracheal tube is known to be a non-linear flow dependent resistance, dependent on many factors including entry effects, laminar flow, turbulent flow and distorted flow profile due to secretions, the position of the tube and the properties of the tube wall (Sly et al. 1996).

The presence of secretions in the tracheal tube tends to decrease flow and increase resistance without any increase in the resistive properties of the underlying respiratory system. Hence measurements of R_{rs} may not accurately reflect modest changes in peripheral airway resistance after therapeutic interventions such as physiotherapy. However, the change in R_{rs} due to the removal of secretions from the upper respiratory tract including the tracheal tube was of particular interest in the current study and changes in peripheral resistance were considered to be less important. Other studies wishing to assess purely the resistive properties of the peripheral respiratory system would have to interpret R_{rs} values with caution. Respiratory system resistance may be a more sensitive outcome following physiotherapy in paediatric patients than in adults because of the relatively larger size of the tracheal tube in relation to the tracheal

diameter and the relatively greater contribution of tracheal secretions to obstruction of the airway.

Tracheal tube diameter, curvature and position also influence R_{rs} and kinks in the tracheal tube will cause an increase in R_{rs}. Thus changes in position after treatment may distort measurements of R_{rs} and mislead with regard to relationships between treatment and changes in R_{rs}. For the purposes of this study, measurements before and after treatment were made in the same position and changes unrelated to the treatment intervention were unlikely to have been significant.

The problems associated with measurements of V_T, C_{rs} and R_{rs} in the presence of tracheal tube leak have been discussed in detail in 5.2.1 and remain a significant issue in ventilated paediatric patients. Moderate to large tracheal tube leaks (>20%) can considerably compromise accuracy and validity of respiratory function measurements in ventilated infants, both by contributing to gross over-estimations in respiratory mechanics and by creating wide within-subject variability in delivered tidal volumes and respiratory mechanics. This variability can contribute to large changes in several measured or calculated parameters after physiotherapy or nursing suction, which may be entirely unrelated to treatment effect. The delivered tidal volume in the presence of tracheal tube leak depends additionally upon the mode of ventilation, with the consequences of tracheal tube leak being worse for patients on volume preset ventilation (Watt and Fraser, 1994).
The magnitude of tracheal tube leak is often not accurately displayed on ventilators or respiratory monitoring equipment, if at all, and the extent to which calculated parameters are inaccurate therefore cannot often be estimated.

7.4.5 Sputum yield

Sputum weight, whether wet or dry, has always been a controversial outcome measure in physiotherapy research because of wide intra- and inter-subject variability. Sputum yield varies during the course of the day in any individual and different pathophysiology will result in different amounts of sputum but not in a predictable or consistent fashion. Age and weight will also influence the volume of sputum produced and, in ventilated patients, volume of instilled saline will influence sputum recovery. While some authors

dispute the correlation between volume of sputum and improved pulmonary function, others suggest that sputum clearance is associated with an improvement in respiratory function. Still others suggest that the connection between sputum production and pulmonary function is irrelevant as long as it can be demonstrated that physiotherapy treatments are advantageous in clearing secretions (see section 1.2.2.1).

The reality is that there is probably some truth in all three of these statements. The relationship between sputum and respiratory function is complex. If the sputum plug is the patients primary problem, removal of it will probably be associated with an improvement in respiratory function. If however, there is additional underlying bronchial reactivity, or haemodynamic instability, the physiological demands imposed by the treatment techniques may result in a temporary deterioration in respiratory function, despite the removal of a plug. There was evidence for both of these clinical scenarios in a number of individuals during the course of this study. In general, removal of thick obstructive material from the airways is considered to be a desirable clinical outcome, even if there is a temporary deterioration in respiratory function, provided that the deterioration is relatively small and short-lived. In these patients, it would appear that sputum, despite being controversial, is the most important and accessible indicator of treatment success.

However, much of the time, in a significant proportion of ventilated children (and adults), secretions are not thick or potentially obstructive, and in these cases the physiological demand imposed by the treatment is less justifiable. Sometimes treatments have re-inflation or recruitment of atelectatic lung segments as primary goals rather than removal of secretions. In these patients, sputum yield is an inadequate and misleading outcome measure, while respiratory function measures would provide more information with regard to the efficacy of treatment.

For physiotherapists to truly understand the beneficial and/or potentially harmful consequences of their treatments, further information is required about the magnitude and duration of these effects and whether anything can be done to prevent or minimise detrimental effects. Measurement of sputum alone would be incapable of providing answers to these questions. However, sputum remains useful adjunct to other measures of respiratory function and adds a depth of understanding to the complexity involved with assessing outcomes to physiotherapy treatment. Sputum measurements additionally help to describe the proportion of patients with copious or minimal secretions and, when

considered in the context of an individuals response to a single and specific treatment, then the issues of wide intra- and inter-subject variability become irrelevant. Thus it remains for many clinicians the most obvious and accessible measure of treatment success in individual patients, especially in the absence of dramatic changes on chest radiograph or auscultation. In this study, although sputum data was collected crudely, the correlation between large (perceived) amounts of sputum and reduction in Rrs suggested that this crude measure might be helpful in predicting treatment effect in the presence of copious secretions (Fig 6-16).

7.4.6 Clinical significance

The difficulty of establishing clinical significance in the presence or absence of statistical significance is an obstacle in medical research. The statistical tools used for scientific rigour are not particularly useful in deciding what makes a tangible difference to patients. Thus although every effort was made in this study to identify changes that were beyond the expected limits of normal variability, it remained difficult to determine whether statistically substantial changes (either improvement or deterioration) made any real clinical difference to patients. Overtly alarming clinical events were extremely rare during measurements, which implies that any statistically significant results demonstrated by this study involved subtle, if any, physiological and clinical signs. It would be very difficult to determine the accumulative influence of these sub-clinical physiological events on the overall course of recovery in the intensive care unit. If these statistically significant changes truly represent negligible clinical events, then the manner in which this type of research is done requires urgent review. Ultimately it would be difficult to justify changes in service provision based on statistical rather than clinical relevance. It is impossible to prove that the benefits of the treatment outweigh the risks if neither the clinical benefits nor risks can be identified.

7.4.7 Immediate outcomes

Data acquired during *in-vivo* studies suggested that as little as 5 minutes would be sufficient to acquire baseline data in paralysed patients. The 15 minute period selected for this study was thus sufficient for assessing baseline values and acute changes in

respiratory function due to physiotherapy or nursing suction. However, this study design was insufficient for assessing delayed changes or prolonged changes in function. If for example, the effects of physiotherapy peaked 80 minutes after therapy, then this may have been missed by the current study. In addition, trends for either improvement or deterioration of respiratory function would be missed by such an approach. Finally, analysis of short term effects of therapeutic interventions may be of limited value to service providers who may be more interested in whether patients who have the intervention get better faster, or go home quicker. Indeed other outcomes, such as quality of life for patients and their families following discharge or long term disability, may be the most relevant issues to address, but are the least accessible in terms of their direct relationship with physiotherapy treatments in intensive care.

Consequently, for future studies, while acknowledging the enormous difficulty in maintaining a reasonably controlled research environment for prolonged periods of time, it would be useful to continue measurements for as long as possible after treatment. Efforts were made in the current study to continue measurements in patients after both physiotherapy and nursing suction, but for various reasons, including medical and nursing interventions, collection of valid data could not be continued indefinitely following treatment. Tidal volume data for example was collected on 89 patients for 15 minutes after physiotherapy. Only 75 of these patients could be followed up for 30 minutes, 42 of these for 45 minutes and 26 of these for an hour. Only 9 patients had continuous measurements without significant clinical interventions for 90 minutes after treatment. This attrition of sample size (due to essential medical or nursing interventions precluding further measurements) is likely to complicate achievement of adequate power over longer periods in future studies.

Some immediate outcomes in this study showed statistically significant changes which suggested at least some of the goals of therapy were achieved (reduction in R_{rs}). They might also suggest the possibility that over the longer term, these therapies might contribute subtly to reducing mortality, morbidity, intensive care unit days or inpatient stay. Hospital stay is influenced by a multitude of factors such as patient age groups, diagnoses, ventilation modalities, variability of physiotherapy and medical therapy options, severity of illness, staffing levels, social class, family circumstances, pressure on

beds as well as significant inter and intra-patient variability. Physiotherapy and nursing suction procedures contribute a relatively small proportion to the management of these patients, and the prohibitively large patient numbers required for a multi-centre randomised controlled trial design to establish the value of these therapies would be impractical, costly and unlikely to guarantee an answer. Thus it appears reasonable to focus research efforts on the acute effects of therapy so that the mechanisms, if any, of therapeutic benefit can be explored. Clinical rather than management questions will be easier to answer in the short term, but ultimately clinical guidelines may be useful in determining managerial decisions.

7.4.8 Study population size and sample

During the data collection period, 144 sets of data were collected on 101 individuals. The scarcity of similar research data meant that prospective power calculations for judging the study sample size were difficult and the magnitude and standard deviations of change between groups could not easily be anticipated. Normal subject variability for selected parameters (in the absence of interventions) was established in section 5.2.2.2. From this, it appeared that many parameters would need to demonstrate at least a 10% change in magnitude before they could be considered significant. The exception was R_{rs}, for which a 20% change was considered desirable. Retrospective power calculations were done to:

- assess whether the sample size in this study had been adequate to detect changes of 10% in all parameters except for R_{rs} in which a difference of 20% was required to show significance.
- provide rough guidelines for sample size in similar studies in the future.

Sample sizes were calculated by Equation 7-1, which is a formula for demonstrating significant effect in one sample of paired differences (for example change following physiotherapy or comparison of nursing suction versus physiotherapy).

Equation 7-1:

$$n > F \times \left(\frac{SD}{d}\right)^2$$

Where n is the number of subjects needed to detect a difference considered to be of scientific or clinical importance (d) between groups with a specified accuracy. SD is the

standard deviation of the differences between groups and F is dependent on the power and significance level required (selected from Table 7-1):

Table 7-1: Value of F depends on power required to detect a difference with specified precision ($p<0.05$)

	Power required			
	80%	90%	95%	99%
Significance level ($p < 0.05$)	7.85	10.51	12.88	18.37

With F taken as 10.51, a false positive result may be expected 5% of the time and detection of a difference (if one exists) may be expected 90% of the time

From Table 5-2 it was felt that a 10% change would be required to demonstrate a change that was significantly different from normal variability in V_{TE}, C_{rs}, VCO_2, $ETCO_2$ and $PeCO_2$ and a 20% change for R_{rs}. Thus the number of subjects needed to detect this magnitude of difference with confidence was calculated (Table 7-2).

Table 7-2: Numbers of subjects needed to detect a 10% change (20% for R_{rs}) at 5% significance with a power of 80%, 90%, 95% and 99%

Parameter	Group mean baseline	SD of the diff between groups	change required	n for 80% power	n for 90% power	n for 95% power	n for 99% power	mean change detected
V_{TE} (mL/kg)	8.27	0.99	0.83	12	16	19	27	0.13
R_{rs} (cmH_2O/L/s)	7.28	34.8	14.6	45	60	74	105	6.90
C_{rs} (mL/cmH_2O/kg)	0.67	0.11	0.068	21	28	34	48	0.01
VCO_2 (mL/min/kg)	4.30	0.54	0.43	13	17	21	29	0.02
$ETCO_2$ (kPa)	5.10	0.63	0.51	13	17	20	29	0.06
$PeCO_2$ (kPa)	3.30	0.35	0.33	9.0	13	16	22	0.06

The study sample (n) recruited was sufficient to detect a 10% change in these parameters with a power of 99%, even when subgroups were analysed. The exception is R_{rs} for which a 20% difference was required to demonstrate a significant change, and for which a slightly greater sample size may have been appropriate.

In retrospect therefore, the 101 subjects recruited to this study were generously adequate to detect significant changes if they existed, even with patients excluded from analysis (for tracheal tube leak >20%) and subgroup analysis for ventilation mode.

Normal variability for $V_{D_{airway}}$, $V_{D_{alv}}$ and $V_{D_{phys}}$ were not established in 5.2.2.2, but using the standard deviations of the observed differences between groups for these parameters, fewer than 20 subjects would be required to detect a difference of 20% ($p<0.05$) significance with a power of 99%. Similarly, fewer than 45 patients were required to detect 20% ($p<0.05$) changes in all arterial blood gas parameters with a power of 99%. The study population in this project was not homogenous, and separate analysis for factors such as ventilation mode, age group or diagnosis meant that the sample size rapidly diminished. However the smallest subgroup for analysis consisted of 20 patients (patients receiving volume preset ventilation), and even this number would have been sufficient to provide 90% power to detect significant changes in the majority of parameters.

The insignificant changes in certain parameters such as V_T and C_{rs} after physiotherapy therefore did not reflect Type 2 errors from inadequate sample size. The likelihood is that these parameters genuinely did not change in any systematic way following treatment. Certain parameters which approached statistical significance such as $PeCO_2$ after physiotherapy ($p = 0.10$) or PaO_2 after nursing suction ($p = 0.12$), demonstrated a tendency for systematic change but of a magnitude that was unlikely to be of clinical significance.

Table 7-3: Numbers of subjects needed to detect 0.5 of a standard deviation change between nursing suction and physiotherapy at 5% significance with a power of 80%, 90%, 95% and 99%

Parameter	Group mean baseline	SD *	change required	n for 80% power (F=7.85)	n for 90% power (F=10.51)	n for 95% power (F=12.88)	n for 99% power (F=18.37)	mean change detected
V_{TE} (mL/kg)	0.11	1.63	0.82	32	42	52	73	0.30
R_{rs} (cmH_2O/L/s)	-7.69	28.3	14.2	32	42	52	73	-7.17
C_{rs} (mL/cmH_2O/kg)	0.01	0.11	0.06	31	42	51	72	0.02
VCO_2 (mL/min/kg)	0.01	0.73	0.36	33	44	55	77	-0.05
$ETCO_2$ (kPa)	-0.07	0.81	0.41	33	44	54	74	-0.15
$PeCO_2$ (kPa)	-0.06	0.60	0.30	33	44	54	74	-0.07

** standard deviation of the difference between groups*

With 82 subjects in the current study, the sample would have had 99% power to detect a significant ($p<0.05$) change of half a standard deviation of the difference between groups if it existed between physiotherapy and nursing suction treatments. While V_{TE}, C_{rs}, $ETCO_2$ and $PeCO_2$ approached significance, in terms of difference in treatment effect, this was not due to inadequate power to detect relatively large changes, but due to the fact that the differences, albeit systematic, were small. The sample was thus adequately powered to detect the larger significant differences between nursing suction and physiotherapy in terms of V_{Dphys}, V_{Dalv}, HCO_3- and O_2 saturation. It could be argued however, that when comparing 2 treatments, somewhat smaller differences could be relevant. The smaller the difference in relation to the standard deviation of the difference, the larger the number of subjects required.

If statistical significance in any parameter could not be achieved with 100 patients, the likelihood of the parameter representing a significant beneficial or detrimental clinical change for the entire group is small. Even results which were substantially significant such as the V_{Dalv} and V_{Dphys} after physiotherapy could not be tangibly related to obvious clinical effects within the group. Nevertheless, the 95% limits of agreement for parameters such as V_{TE}, R_{rs} and C_{rs} indicate that there may have been significant changes within individual patients. In addition, any intervention which has the potential to do great harm, even to a very small minority of patients, should be identified as a risk factor for that minority. It would be important for a study with such an aim to have sufficient numbers to encounter these risk factors. No dramatic clinical consequences were observed after any treatment during the course of this study.

The current study has demonstrated the sensitivity of various parameters to physiotherapy or nursing suction in fully ventilated children and this is potentially valuable information in identifying parameters that could be sensitive enough to be related to clinical change. For parameters such as deadspace the significant results demonstrate a potentially exciting outcome not previously explored in physiotherapy research. Future studies should be directed towards finding ways of exploring the clinical impact of outcomes which appear to be sensitive to interventions such as physiotherapy. Although it may be argued that simultaneous study of multiple parameters can lead to Type I errors, the nature of respiratory function is such that the

simultaneous interactions between variables can add greater levels of understanding between and within each other. For example, none of the outcomes in this study would have been valid unless the effects of tracheal tube leak had been assessed. $V_{D_{phys}}$ needs to be understood in the light of V_T and C_{rs} needs to be assessed relative to leak and V_T as well as ventilation mode.

The exclusion of all but paralysed patients from this study meant that results were only obtained in a particularly narrow spectrum of paediatric intensive care patients. This limits the extrapolation of results to a more general paediatric population. Furthermore, the criteria for pharmacological paralysis in this hospital appeared to generate specific subgroups of populations for example following cardiac or gastric transposition surgery or patients with head injury. There is the potential for this sort of selection to have influenced the results systematically. Patients following cardiac surgery for example might be expected to have significant intra-cardiac shunt and changes in V/Q relationships, and thus have greater baseline $V_{D_{alv}}$ than general paediatric intensive care unit patients. There were however no significant differences in response to treatment when results were analysed according to diagnostic groups and it appears reasonable to extrapolate results of this study to other paralysed fully ventilated paediatric populations. Differences in response to treatment are probably likely to depend on factors such as severity of illness, haemodynamic stability or bronchial hyper-responsiveness rather than diagnosis alone. The theoretical advantage of data collection in specific patient groups is that inferences can be made about the way in which that specific population responds to physiotherapy or nursing suction.

The inclusion criterion for patients to be muscle relaxed and fully ventilated ensured collection of reliable data (in the absence of tracheal tube leak) from which inferences could be made about the effects of physiotherapy or nursing suction as well as allowing valid measurements of respiratory mechanics. However, it is relatively rare for patients in our intensive care units to be paralysed and fully ventilated. Thus very little information has been obtained about the effects of physiotherapy or nursing suction on the majority of paediatric intensive care unit admissions. What can be deduced from available literature is that patients less well sedated would be likely to demonstrate greater anxiety and suffer a larger metabolic demand from treatment. Increases in

respiratory rate, heart rate, blood pressure and V_T would be generated from patient effort and these would complicate analysis of respiratory function data. While these appear to suggest a larger physiological debt, patients who are less well sedated tend to have greater cardiovascular stability and would potentially tolerate treatment better. In general however, paralysed fully ventilated patients are entirely different to those with assisted ventilation and it would not be advisable to extrapolate results between these groups. Since these two populations probably require to be studied separately in terms of the influence of physiotherapy on respiratory function, it is not critical that the results of this study be extrapolated to self-ventilating children. Future studies would need to identify appropriate outcomes valid for non-paralysed children with assisted ventilation, including respiratory rate and a measure of work of breathing.

7.4.9 Observation effect and heterogeneity between staff populations and therapy procedures

The fact that the nurses and physiotherapists involved were aware they were being observed might have altered their normal practice slightly. The effect in general for both professional groups would probably be to bias performance towards "best practice". It remained of interest however to investigate how "best practise" physiotherapy interventions compared with "best practise" nursing interventions in terms of effects on respiratory function. In all probability observer bias became insignificant as the study progressed, although this would have occurred more quickly for physiotherapy treatment since there were far fewer staff involved. It is unlikely that this effect would have had any statistically significant effect on outcome.

The combined paediatric and cardiac intensive care units at Great Ormond Street Hospital had approximately 130 nursing staff members. By contrast, the physiotherapy department had fewer than 25 staff who would be called upon to work in the intensive care environment. Of these approximately 3 were full time senior staff members and 3 were senior staff on 6 month clinical rotations through the units. Thus during the data collection period, it is unlikely that more than 15 physiotherapy staff members were involved with treatments, while it is likely that about 4 times this number of nursing staff

would have performed treatments during respiratory function measurements. There is a theoretical risk with such heterogeneity of staff populations that the variability of skills and experience would be greater in the nursing staff population and that this variability could potentially have influenced the outcome of this study.
This risk is offset by the fact that the proportional representation of nursing and physiotherapy staff in this study was probably similar to other units in this and other countries. This heterogeneity thus reflects a clinical reality in terms of staff populations, which, if corrected for in a research study might produce misleading results.
Furthermore, data with regard to physiotherapy and nursing levels of experience were informally and crudely collected. Staff who had worked in the units for over one year were considered to be experienced, staff who had only worked in the unit for three months to a year were considered to be moderately experienced while staff employed for less than three months were considered to be inexperienced. Multivariate analyses were performed to assess any overt relationship between these 3 levels of experience in both nurses and physiotherapy staff and whether patients had statistically significant improvement, deterioration or no change, in selected parameters. No relationship was observed, suggesting that other variables, probably relating to the individual and time specific circumstances of each patient were more likely to influence the outcome of the treatment, provided that essentially competent treatments were performed by both physiotherapy and nursing staff.

Physiotherapy and suction techniques vary considerably between institutions and countries. It is thus impossible to generalise or extrapolate results to institutions where policies on airway clearance are dissimilar.

7.5 What are the future directions ?

Future studies should attempt to identify factors linking patients who respond favourably to physiotherapy, so that patient selection criteria can be established which are easily available to clinicians. The ANOVA procedures performed in this study were largely unsuccessful at determining common factors between patients who improved or deteriorated after treatment. The failure of these analysis procedures may have been a reflection on inadequate power within subgroups, or of the fact that other variables

which were not prospectively collected (such as pulmonary artery pressure, severity of illness scores or oxygenation or ventilation indices) may have been more useful. Future studies should also attempt to identify more sensitive reference variables. Outcome parameters sensitive to different types of ventilatory assistance, the presence or absence of leak and spontaneous versus paralysed patients will all need to be established.

Future studies should attempt to differentiate the individual effects of different treatment modalities on respiratory function. If, for example, it was conclusively shown that tracheal tube suction alone produced a reduction in V_T and C_{rs}, while manual hyperinflation improved both V_T and C_{rs}, it would be simple to recommend practice in which the necessary but potentially deleterious effects of suction were minimised by ending the treatment with a period of hyperinflation.

The randomised crossover design in this study was particularly effective in controlling for the multitude of variables in ventilated patients that may have made comparisons between patients difficult and this will remain a useful study design in future. Repeated measures would also be helpful to identify whether within-subject responses to second or third physiotherapy or nursing treatments are consistent in selected patients.

Intra-arterial fibre-optic blood gas monitoring systems offer on-line information on oxygenation, ventilation, and acid-base status and allows immediate detection of acute and potentially life-threatening events (Numa and Newth, 1995; Kilger et al. 1995). These devices have been shown to be accurate in paediatric populations (Weiss et al. 1996; Weiss et al. 1999; Macintosh and Britto, 1999), and, when inserted through a peripheral intravenous cannula, the Paratrend monitor can be used to provide an accurate estimation of arterial blood gas values in children with respiratory failure (Tobias et al. 1998; Tobias et al. 2000).

Ideal respiratory monitoring devices would accurately display tracheal tube leak and calculate compliance separately during the expiratory and inspiratory phases of each breath. There are now a multitude of measurement tools available for assessing respiratory function in ventilated patients and as technology advances, the accuracy and validity of these will improve even for difficult patient groups, for example, those on

high frequency ventilation, or those with extremely low volumes and flow for example ECMO patients. Ultrasonic flowmeters, infrared gas analysers, SF_6 multiple breath washout and oscillation mechanics all hold promise for the future (Schibler et al. 1997, Schibler et al. 2000).

7.6 Overall summary

This study has established that the "CO_2SMO Plus" is a valid, reliable and potentially useful tool for monitoring specific respiratory function parameters in muscle relaxed, fully ventilated paediatric patients. It has also explored group and within-subject changes in selected parameters due to respiratory physiotherapy treatments. In addition, it has clarified differences between the physiological effects of physiotherapy and suction alone and thus suggested the potential and distinct advantages of both therapies. Finally, although this study has not contributed substantially to the overall understanding of the clinical importance of these physiological effects, it has addressed the limitations of respiratory function measurements in ventilated patients and attempted to interpret results objectively within those limits. In this respect at least, this study is distinguishable from the majority of other similar studies and should potentially offer a base-line position from which future research may benefit.

"I don't have any solution but I certainly admire the problem."

Ashleigh Brilliant

8. Publications related to the current study.

8.1 *Sternal closure paper, Critical Care Medicine, 2001*

Pediatric Critical Care

Effect of delayed sternal closure after cardiac surgery on respiratory function in ventilated infants

Eleanor Main, MSc; Martin J. Elliott, MD; Margrid Schindler, MB BS; Janet Stocks, PhD

Objective: Studies examining the effect of sternal closure on respiratory function have not been published, and currently there is little evidence to guide ventilation management immediately after closure. The aim of this study was to establish the impact of delayed sternal closure on expired tidal volume, respiratory system compliance, and CO_2 elimination immediately after the procedure in infants who had undergone open heart surgery.

Design: Prospective study of respiratory function before and after delayed sternal closure.

Setting: Cardiac intensive care unit, Great Ormond Street Hospital, London.

Patients: Seventeen infants (median age, 2 wks) with open median sternotomy incisions after cardiac surgery. Data were collected between August 1998 and March 2000.

Interventions: Respiratory function was measured continuously for 30 mins before and after delayed sternal closure in paralyzed ventilated infants.

Measurements and Results: Four babies were excluded from the study because they required either immediate increase in ventilation after delayed sternal closure (n = 3) or removal of pericardial blood collection (n = 1). In the remaining 13 infants, expired tidal volume and CO_2 elimination decreased significantly ($p < .005$) by a mean of 17% and 29%, respectively, after sternal closure. In five of the remaining 13 patients, the magnitude of tracheal tube leak increased by ≥10% after delayed sternal closure, thereby invalidating recorded changes in respiratory system compliance. Of the eight infants in whom there was a minimal change in leak, respiratory system compliance decreased significantly ($p < .05$) by a mean of 19%.

Conclusions: This study supports the hypothesis that respiratory function may be compromised after delayed sternal closure and that ventilatory support should be increased to counteract the anticipated decrease in tidal volume. Extra vigilance should be applied in monitoring blood gases after delayed sternal closure to assess clinical responses to sternal closure or changes in ventilatory support. Accurate assessment of change in respiratory system compliance after any therapeutic intervention may be precluded by changes in tracheal tube leak during the procedure. (Crit Care Med 2001; 29:1798–1802)

KEY WORDS: respiratory mechanics; mechanical ventilation; cardiopulmonary interaction; intensive care unit; respiratory compliance; respiratory resistance; cardiac surgical procedures; cardiopulmonary bypass; human; infant; newborn; postoperative care; respiration; artificial; sternum; surgery; treatment outcome; neonates; postoperative period; pulmonary; hemodynamics; postoperative complications.

Early repair of complex congenital heart malformations such as transposition of the great arteries, total anomalous pulmonary venous drainage, and complete atrioventricular septal defects may lead to life-threatening respiratory and hemodynamic dysfunction when sternal closure occurs. Intraoperative development of myocardial and pulmonary edema contributes to this effect. To avoid a fatal outcome in these situations, the surgeon may postpone sternal closure for several hours or days until edema has reduced and cardiopulmonary stability has been achieved. This procedure, with optimal inotropic and ventilatory assistance, can provide the necessary interim support vital for ultimate survival (1, 2). Delayed sternal closure (DSC) in this article refers to closure of the sternal edges, fascia, and skin.

When eventually performed, DSC may alter ventilatory variables immediately after the procedure, suggesting that closure may be associated with a temporary decline in pulmonary function related to a reduction of intrathoracic volume. Recently, a retrospective study reported significant increases in peak inspiratory and mean airway pressures after DSC, although ventilation modalities and tracheal tube type were not specified (3). However, no prospective studies to date have quantified the change in pulmonary variables associated with DSC. Consequently, changes in ventilatory support may be randomly and inconsistently applied, with or without the guidance of arterial blood gas values.

Several authors have contended that respiratory measurements in ventilated patients may assist in evaluating responses to therapeutic or clinical interventions or optimizing ventilation (4–9). Such measurements have become more feasible now that pressure and flow transducers commonly are integrated into modern ventilators and respiratory monitors.

This study was undertaken to measure the degree, if any, of pulmonary compromise caused by DSC so that recommendations might be explored in terms of optimizing ventilatory management after this procedure. The aim of this study was

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to assess the influence of DSC on expired tidal volume (V_{TE}), volume of CO_2 eliminated (V_{CO_2}), and total respiratory system compliance (C_{rs}) in mechanically ventilated infants who had undergone open heart surgery.

MATERIALS AND METHODS

Data were collected between August 1998 and March 2000 in the cardiac intensive care unit at Great Ormond Street Hospital for Children NHS Trust, London. Written informed consent for respiratory function monitoring was obtained from the parents of all infants included in the study.

The CO_2SMO Plus respiratory monitor (version 3.0; Novametrix Medical Systems, Wallingford, CT) was used to measure respiratory variables continuously in 17 ventilated infants (nine male, eight female) with open median sternotomy incisions before and after delayed closure following surgery for the cardiac malformations listed in Table 1. The median age at measurement was 2 wks (range, 3 days to 3 yrs), and median weight was 3.1 kg (range, 2–16 kg). V_{TE}, V_{CO_2}, and C_{rs} were determined continuously for 30 mins before and after DSC, during which time ventilator pressures and rate were not modified (Fig. 1). All 17 babies were ventilated on pressure preset modalities because all had uncuffed tracheal tubes with variable leaks, thereby precluding the use of volume preset ventilation. Infusions of vecuronium, midazolam, and morphine provided muscle relaxation, sedation, and analgesia, respectively. Because none of the babies were making independent respiratory efforts, measurements of C_{rs} could be made by using pressure changes at the airway opening without additional esophageal manometry (10). The infants also had continuous monitoring of arterial hemoglobin oxygen saturation (Sa_{O_2}), intrasystemic arterial pressure, and electrocardiogram. Arterial blood gas analysis was performed within 1 hr before and repeated within 1 hr after sternal closure. Increased ventilatory requirements (pressures, rate, or delivered oxygen concentration) during this period were noted. Data obtained were stable with little variability except for the tugging and movement created by the surgical procedure.

The CO_2SMO Plus measures pressure, flow, and CO_2 concentration continuously via a disposable, fixed-orifice, differential pressure flow sensor inserted between the tracheal tube and the ventilator circuit. A neonatal sensor with combined apparatus deadspace of 0.7 mL was used in all infants studied. Pressure and flow were measured instantaneously across the flow sensor with no time lag. Data were recorded electronically by a 20-bit resolution, 100-Hz flow data sampling microprocessor. During repeated calibration checks of the neonatal sensor with the tracheal tube *in situ* (11), the mean (SD) measurement error was found to be 1.3 (1.9%) over a volume range of 2–300 mL (Hans-Rudolf calibrated syringes, Kansas City, MO). The mean coefficients of variation for repeated *in vitro* measurements were 2.6% and 2.4%, respectively, for inspired tidal volume (V_{TI}) and V_{TE}, whereas mean percentage errors for V_{TI} and V_{TE} were 2.2% (1.6%) and 0.8% (2.9%), respectively. Similarly, calibration checks of the pressure transducers revealed that measurements were within 3% of applied pressure over a range of 2–60 cm H_2O (0.2–5.9 kPa).

V_{TI} and V_{TE} were calculated separately by digital integration of flow. Exhaled volume was used for both V_{TE} and V_{CO_2} calculations in this study (12). By contrast, C_{rs} was computed automatically with the CO_2SMO Plus by applying the least squares regression method to all volume, pressure, and flow data points throughout the whole breath cycle. The use of multiple linear regression is now widely recognized as one of the most appropriate methods of measuring respiratory mechanics in ventilated infants because it does not require any special ventilator setting or maneuvers and allows C_{rs} and respiratory system resistance (R_{rs}) to be determined on line on a breath-by-breath basis during ongoing mechanical ventilation (10, 13). V_{CO_2} was calculated as the net volume of exhaled CO_2 measured at the tracheal tube over each minute. This value was divided by the weight of the infant and expressed in milliliters per minute per kilogram. V_{TE}, C_{rs}, and V_{CO_2} were recorded and saved as average values for each minute of recording. Data were analyzed by assessing both individual responses to DSC (30 data points before and after sternal closure) in each infant and group mean differences by using the standardized Student's *t*-test. Because numbers were small, group differences were confirmed by a Wilcoxon comparison.

Ventilation index (VI) and oxygenation index (OI) were calculated before and after DSC by using the following formulas:

$$VI = \frac{Paco_2 \text{ (mm Hg)} \times PIP \text{ (cm } H_2O) \times \text{respiratory rate (bpm)}}{1000}$$

$$OI = \frac{MAP \text{ (cm } H_2O) \times Fio_2 \times 100}{Pao_2 \text{ (mm Hg)}}$$

Tracheal tube leak potentially can affect measurements of respiratory function (12, 14–17). We therefore assessed the magnitude of the tracheal tube leak throughout the measurement periods to assess its influence, if any, on calculated values of V_{TE}, V_{CO_2}, and C_{rs}. Tracheal tube leak expressed as a percentage was calculated as the difference between inspired and expired tidal volume by using the following equation:

$$\% \text{ leak} = \frac{(V_{TI} - V_{TE})}{V_{TI}} \times 100$$

Table 1. Diagnoses

Diagnosis	No.
Transposition of the great arteries	6
Complex cardiac defects	4
Total anomalous pulmonary venous connections	2
Truncus arteriosus	2
Hypoplastic left heart	2
Interrupted aortic arch	1
Total	17

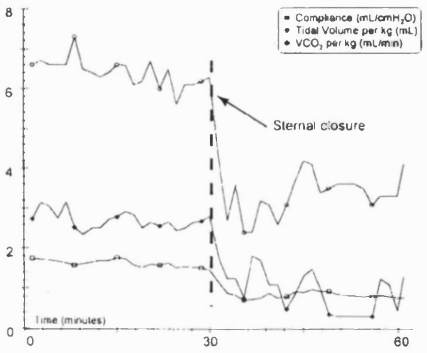

Figure 1. Sixty-minute trend in recorded data during sternal closure in a 2-wk-old (3.3-kg) infant. *VCO_2*, volume of CO_2 eliminated.

RESULTS

Three babies were excluded from the study because they exhibited sudden deterioration in Sa_{O_2} or hemodynamic instability, requiring immediate increase in ventilatory support with DSC. A further infant was excluded because a large pericardial collection of blood was removed during DSC. This was accompanied by an immediate clinical improvement, thereby precluding interpretation of the effects of DSC. In the remaining 13 infants, V_{TE} and V_{CO_2} decreased significantly ($p <$

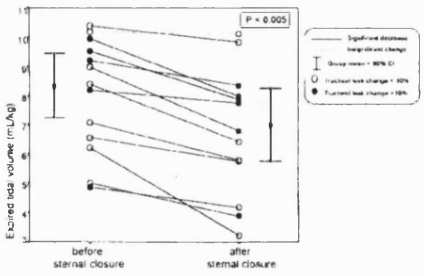

Figure 2. Tidal volume: Individual and group changes in response to delayed sternal closure (n = 13). *CI*, confidence interval.

.005) by a mean of 17% (range, −48% to 5%) and 29% (range, −69% to −5%), respectively, after DSC (Figs. 2 and 3).

All infants in this study had uncuffed tracheal tubes, and there was a significant ($p < .05$) increase in tracheal tube leak immediately after delayed sternal closure (Table 2, Fig. 4). In five of 13 cases, the magnitude of leak increased by ≥10% immediately after closure, thereby invalidating the determination of C_{rs}. Of the eight infants in whom there was a minimal change in leak, C_{rs} decreased significantly ($p < .03$) by an average of 19% (range, −49% to 12%) (Fig. 5). The extent to which changes in leak affected the results is shown in Table 2, which summarizes changes in VTE, Vco_2, and C_{rs} for the entire group (n = 13) and for those in whom the tracheal tube leak changed by <10% during the procedure. Although values of VTE and Vco_2 showed a slightly greater reduction after DSC for the whole group than after we excluded those in whom leak increased significantly, the direction and significance of this change remained the same. By contrast, had these infants not been excluded, interpretation of the effects of DSC on C_{rs} would have been totally confounded.

When we inspected clinical parameters for all 17 infants undergoing DSC, Sao_2, heart rate, and mean arterial blood pressure remained within acceptable limits during the procedure, although mean arterial blood pressure decreased significantly ($p < .05$) by an average of 4 mm Hg after DSC (Table 3). After DSC, there was a statistically significant increase in VI by an average of 12%. This may not have been clinically significant because arterial pH did not decrease below 7.35 in any of the infants (Table 3). A similar tendency was seen for OI, although this just failed to reach significance ($p = .07$). After DSC, there were clinical indications to increase mechanical ventilation in nine (53%) infants (three immediately and six within 1 hr of DSC). Ventilator settings remained unchanged in seven infants and were decreased in one infant who had a stage 1 Norwood procedure in whom the Sao_2 increased after DSC.

DISCUSSION

Results from this study show that three of 17 patients did not tolerate sternal closure at the level of ventilatory support they were receiving before the procedure, and that with the exception of an infant in whom a large pericardial blood clot was removed, VTE and Vco_2 decreased significantly as a result of DSC ($p \leq .01$; Figs. 2 and 3). The deterioration in VI and the need for increased ventilation in 53% of infants within 1 hr of sternal closure suggest that the observed reductions in VTE, Vco_2, and C_{rs} were clinically significant.

Although many factors other than sternal closure could have influenced VTE, Vco_2, or C_{rs}, most of these would have a slower onset than the immediate changes observed in the current study. Furthermore, no patients had any evidence of pulmonary hemorrhage, edema, atelectasis, or changes in chest radiograph before DSC, because this would have precluded closure. Similarly, no patients had pulmonary hemorrhage or any acute changes on chest radiograph after DSC. Consequently, the acute changes observed (Fig. 1) that occurred instantaneously after chest closure were most likely to be attributable to the procedure itself rather than any other cause.

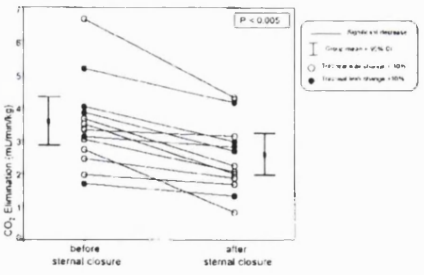

Figure 3. CO_2 elimination: Individual and group changes in response to delayed sternal closure (n = 13). *CI*, confidence interval.

The potential influence of the increase in tracheal tube leak must be taken into account when interpreting these results. During baseline measurements, the leak was <20% in all but one of the infants, a level generally found to be compatible with accurate measurements of respiratory function in infants (17). There was a significant increase in tracheal tube leak after DSC, which exceeded 10% (range, 10.2% to 23%) in five of the infants and which was probably attributable to the reduction in C_{rs} after sternal closure. Under these conditions, relatively more air will be shunted across the leak pathway during inspiration than into the stiffer lungs, resulting in an overestimation of VTI. Such pressure-dependent errors are far less marked during passive expiration, and it is therefore recommended that estimates of tidal volume always be based on VTE, as in this study. Indeed, the relative reductions in both VTE and Vco_2 (which also were based on expired volumes) were similar in those with and without any change in leak (Table 2), suggesting that these were relatively robust outcome measures that reflected the true clinical situation of decreased ventilation. By contrast, interpretation of C_{rs} in the presence of leak is more complex. The CO_2SMO Plus, like many current available systems for assessing respiratory mechanics in ventilated patients, bases calculation on least squares regression over the whole breath (18). Although this remains one of the more robust methods of calculation, it nonetheless will overestimate C_{rs} in the presence of large leaks (14). Any overestimation of VTI will be reflected in an overestimation of

Table 2. Changes in expired tidal volume (VTE), volume of CO_2 eliminated (Vco_2), total respiratory system compliance (C_{rs}), and leak after delayed sternal closure (DSC)

	Whole Group (n = 13)			<10% Change in Leak (n = 8)		
	Before DSC[a]	After DSC[a]	95% CI	Before DSC[a]	After DSC[a]	95% CI
VTE	8.27 (1.69)	6.98 (2.12)	−1.88 to −0.69[b]	7.79 (1.86)	6.48 (2.48)	−2.21 to −0.41[c]
Vco_2	3.60 (1.26)	2.55 (1.00)	−1.48 to −0.62[b]	3.40 (1.43)	2.25 (1.04)	−1.80 to −0.50[b]
C_{rs}	0.74 (0.22)	0.82 (0.54)	−0.14 to 0.29	0.63 (0.14)	0.52 (0.21)	−0.20 to −0.02[c]
Leak	15.0 (4.16)	21.6 (9.51)	1.18 to 12.2[c]	15.1 (3.76)	16.2 (5.94)	−0.87 to 3.09

95% CI, 95% confidence intervals of the difference (after −before DSC) in mean values.
[a]Results are expressed as mean (SD); [b]$p < .005$; [c]$p < .05$.

C_{rs}, thereby masking any clinical reduction in this parameter. Several lung and animal model studies have established that calculated C_{rs} is proportionately related to tracheal tube leak and is grossly overestimated with increasing magnitude of leak (12, 14, 15, 17).

Although it has been suggested that the use of the expiratory portion of each breath to calculate respiratory mechanics might reduce the confounding effect of leak (10, 12, 14), this was not available on CO_2SMO Plus at the time of data collection. In addition, this approach has yet to be validated and potentially is fraught with difficulties, particularly in the presence of any alinearities of the respiratory system. Calculated values of C_{rs} that are recorded in the presence of a significant leak, or change in leak, therefore must be interpreted with caution. In this study, there was a strong positive relationship between change in leak and change in C_{rs} (r^2 = .64). Thus, when the potential effect of leak was disregarded, there was no significant change in C_{rs}. By contrast, when the five infants in whom leak had increased by >10% were excluded, a significant ($p < .05$) decrease in C_{rs} was observed (Table 2).

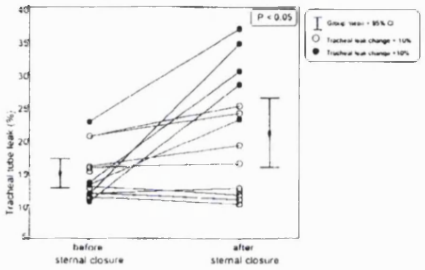

Figure 4. Tracheal tube leak: Individual and group changes in response to delayed sternal closure (n = 13). *CI*, confidence interval.

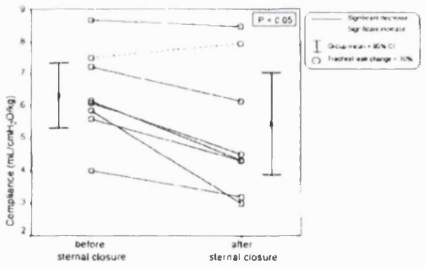

Figure 5. Compliance: Individual and group changes in response to delayed sternal closure in those in whom tracheal tube leak changed by <10% (n = 8). *CI*, confidence interval.

Uncuffed tracheal tubes commonly are used to ventilate infants and children because of concerns about subglottic damage, but the confounding influence of tracheal tube leaks can be a real disadvantage in terms of objectively assessing therapeutic interventions. When a substantial leak exists with concurrent overestimation of VTI and hence C_{rs}, it is impossible to assess the magnitude or direction of any physiologic changes in respiratory mechanics, although the magnitude of the error will depend, to some extent, on the precise method of calculation (15). Any attempt to use measurements of C_{rs} to evaluate therapeutic interventions or to detect within-subject changes in clinical status would require negligible leak throughout the study period (17). Although such a condition may not be attainable unless a cuffed tube is *in situ* (4), many publications reporting respiratory mechanics in ventilated infants and children have failed to report either the change in or magnitude of this vital confounding factor. Unfortunately, significant leaks are not always audible or clinically obvious, nor is their magnitude accurately reported (if at all) on most monitors or ventilators.

The three babies excluded from this study because of the need for immediate increase in ventilatory support had all received relatively low baseline tidal volumes before the procedure when compared with the remaining infants (mean 5.9 mL/kg compared with mean 8.3 mL/kg). This suggests that the levels of ventilatory support immediately before closure may have been only just sufficient to cope with current clinical conditions, with no buffer with which to tolerate any sudden deterioration in respiratory mechanics. The early and severe respiratory compromise evidenced by these three babies emphasizes the need for increased vigilance during and after sternal closure.

Infants in this study were ventilated with pressure preset modes because of their age and the fact that they had uncuffed tracheal tubes. Had cuffed tracheal tubes been used, volume preset modes may have proved more robust against the decrease in respiratory compliance experienced after sternal closure. However, a decrease in compliance after sternal closure would manifest in an increased peak inspiratory pressure required to maintain the same volume with concurrent risk of barotrauma. In this study, the median age at measurement was 2 wks, an age group in which pressure preset ventilation often is preferred above volume ventilation so that ventilator-induced lung injury may be avoided. Regardless of ventilatory mode, a moderate to large tracheal tube leak would confound interpretation of compliance calculations and make it difficult to provide optimal and consistent levels of ventilation and positive end-expiratory pressure (19). Whereas normal practice in our unit has been to increase mechanical ventilation by 10% to 20% before DSC in anticipation of any deterioration in mechanics during the procedure, no objective evidence as to whether this practice was necessary was available. Because interpretation of changes in tidal volume, $V\dot{C}O_2$, and C_{rs} will be confounded by changes in ventilator settings, the latter were held constant for the purposes of this study and were increased only if clinically indicated by close monitoring of the infants. The results of this study support the practice of increasing ventilatory support before DSC, especially in infants with uncuffed tracheal tubes with pressure preset ventilation.

Table 3. Effect of delayed sternal closure (DSC) on clinical variables (n = 17)

Variable	Before DSC[a]	After DSC[a]	95% CI
Arterial oxygen saturation	93.4 (6.14)	94.0 (6.45)	−1.8 to 3.1
Heart rate	151 (18.1)	156 (16.8)	−2.3 to 11.5
Mean arterial blood pressure	56.0 (9.63)	52.4 (6.78)	−7.2 to −0.1[b]
pH	7.47 (0.05)	7.45 (0.06)	−0.07 to 0.02
Ventilation index	17.1 (4.99)	19.1 (7.00)	0.3 to 3.7[b]
Oxygenation index	3.59 (1.26)	4.41 (1.81)	−0.1 to 1.9[c]

95% CI, 95% confidence interval of the difference (after − before DSC) in mean values.
[a]Results are expressed as mean (SD); [b]$p < .05$; [c]$p = .07$.

CONCLUSIONS

This study supports the hypothesis that respiratory function may be compromised after sternal closure and highlights the difficulty in objectively assessing therapeutic interventions in ventilated infants and children.

When sternal closure is imminent, ventilatory support should be increased to counteract the anticipated decrease in

This study supports the hypothesis that respiratory function may be compromised after sternal closure and highlights the difficulty in objectively assessing therapeutic interventions in ventilated infants and children.

tidal volume. Extra vigilance should be applied in monitoring blood gases after DSC to assess clinical responses to sternal closure or changes in ventilatory support.

Assessment of C_{rs} in response to any therapeutic intervention will be prevented by a change in tracheal tube leak. Further studies may benefit from the use of cuffed tracheal tubes.

In future, it is essential that ventilators and monitors provide a continuous and accurate display of the magnitude of leak and that this is documented whenever measures of C_{rs} are reported.

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The influence of endotracheal tube leak on the assessment of respiratory function in ventilated children

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Abstract. *Objective*: The use of respiratory mechanics to optimise ventilator settings has become more common since the integration of pressure and flow transducers into modern ventilators. However, values of respiratory resistance (R_{rs}) and compliance (C_{rs}) can be overestimated in the presence of tracheal tube leak and clinical decisions based on these figures would be misinformed. This study aimed to assess the influence of tracheal tube leak on measurements of C_{rs}, R_{rs} and expired tidal volume (V_{TE}) in ventilated children in order to establish when such measurements were reliable in this population. *Design*: Respiratory function was monitored for at least five consecutive hours during which normal medical procedures were performed. The magnitude and variability of tracheal tube leak was assessed during these periods. *Setting*: The paediatric and cardiac intensive care units at Great Ormond Street Hospital for Children, NHS Trust, London. *Patients*: Seventy-five paralysed, fully ventilated infants and children. *Results*: Ten children had a mean leak greater than 20% (range: 22%-65%). Amongst this group there were wide fluctuations with respect to leak magnitude, V_{TE}, C_{rs} and R_{rs}. Leaks of less than 20% appeared necessary to obtain reliable measurements of C_{rs} and R_{rs} and to ensure consistent and adequate ventilation. *Conclusions*: Leaks larger than 20% result in inconsistent tidal volume delivery and gross overestimation of C_{rs} and R_{rs} irrespective of ventilation mode. The magnitude of tracheal tube leak needs to be accurately displayed on all ventilatory equipment to verify reliable measures of respiratory function so that appropriate clinical decisions can be made and ventilatory management optimised.

Keywords. Ventilators, mechanical - Respiration, artificial - Intubation, intratracheal - Respiratory function tests - Respiratory mechanics - Child

Introduction

In the last decade, several authors have noted the potential for respiratory measurements in ventilated patients to assist in optimising ventilation, by reducing iatrogenic lung damage from lung over-distension and hastening the clinicians' response time to clinical changes. In addition, sheer stress on the lungs can be avoided by ventilating with appropriate tidal volumes and optimal levels of PEEP (1-6). The use of respiratory mechanics to guide clinical ventilatory management has become more common since the integration of pressure transducers into modern ventilator equipment and respiratory monitors. Many ventilators now display respiratory parameters such as resistance and compliance and intensivists therefore have on-line information about the respiratory function of their patients. If there is any intention to act on these readily displayed figures, it is essential to examine their accuracy and the conditions under which they might become unreliable. Data about the accuracy of measurement devices and the validity of calculated parameters are seldom given in specification manuals, and information about restricted applicability or conditions under which the measurement and calculation of the parameters may become erroneous are limited. One confounder, which has been identified in laboratory and animal studies and which is especially pertinent to paediatric ventilation, is the tracheal tube leak. Uncuffed tracheal tubes are commonly used to ventilate infants and children because of concerns about subglottic damage. However there is relatively little information with regard to the effects of leak in the clinical environment or how much leak may be tolerable in ventilated children. Tracheal tube leak can confound a number of parameters of interest, including metabolic gas exchange and functional residual capacity (7,8). Krauel et al showed that patients with a tracheal tube leak needed higher FiO_2, MAP and respiratory frequency than those without such a leak (9). Tracheal tube leak has been found to reduce the mean tracheal pressure with respect to the mean airway pressure by 15-21% in rabbits (10). The predictive value of MAP in guiding clinical decisions is thus reduced in the presence of leak. Furthermore any increase in the magnitude of tracheal tube leak may result in a disproportionate decrease in oxygenation by decreasing mean tracheal pressure, and a reduction in the efficiency of tidal ventilation and lung recruitment via PEEP. In the presence of lung disease and reduced compliance, gas shunting through the leak pathway is likely to increase, which may further compromise ventilatory support. In diseased lungs, even small airway leaks lead to large reductions in lung recruitment at

higher PEEP values, and errors in measuring resistance and compliance have been found to be relatively larger than in healthy lungs for all magnitudes of leak (11).

Several lung model or animal model studies have established that compliance and resistance measurements are overestimated and unreliable in the presence of leak (11-13). While these are valuable in-vitro results, caution should be exercised when extrapolating these findings to the clinical setting. Kuo et al noted that while errors were proportionate to the size of the leak, they also depended on the method used to calculate respiratory mechanics (13). The most commonly used techniques include Mead and Whittenberger's method, multiple linear regression analysis or the least squares method (14).

The aim of this study was to assess in vivo the influence of tracheal tube leak on expired tidal volume (V_{TE}), respiratory compliance (C_{rs}) and respiratory resistance (R_{rs}) in ventilated children and infants. In addition the magnitude and within-subject variability of tracheal tube leak was assessed in order to establish when such measurements could be performed reliably in this population.

Materials and Methods

The "CO_2SMO Plus" respiratory monitor (Novametrix Medical Systems Inc. USA, version 3.0) was used to measure respiratory function continuously in 75 paralysed, ventilated babies and children between May 1998 and August 1999. Inclusion criteria were that patients were muscle relaxed, fully ventilated and were unlikely to have changes in ventilatory parameters for the duration of measurement. A range of ventilators including Bear Cub BP2001, Servo 300 and 900 and SLE 2000 were used, with the pressure pre-set modalities preferentially used in young babies and both volume and pressure pre-set modalities used in older children. No patients were excluded from analysis and data from the entire measurement period were analysed for all patients. The "CO_2SMO Plus" measures pressure, flow and capnography continuously via a disposable fixed orifice differential pressure flow sensor connected between the tracheal tube and the ventilator circuit. The flow sensor was attached and taped firmly to the mouth of the tracheal tube thereby avoiding the possibility of leak at this junction. A neonatal sensor (combined apparatus deadspace 0.8 ml), was used in children less than 2 years, whereas a paediatric sensor (deadspace < 4 ml) was used in older children. Pressure and flow were measured instantaneously across the flow sensor with no time-lag. Data were electronically recorded by a 20 bit resolution, 100 Hz flow data sampling microprocessor and transferred to Analysis Plus software on a portable PC running Analysis Plus! software version 3.0 (Novametrix Medical Systems, Wallingford, CT).. Repeated calibrations of the sensors over appropriate volume ranges (2 - 300 ml for neonatal sensors and 40 -500 ml for the paediatric or adults sensors) demonstrated that on average the sensors were capable of measuring applied volume changes within 0.9 % (SD: 2.3 %) accuracy. Furthermore these tests showed that on average, inspired volumes differed by less than 2 % (SD: 2.3 %) against expired volumes when assessed in vitro (Table 1). This accuracy was maintained when calibration was repeated after connecting appropriately sized tracheal tubes (Table 1). Similarly pressure recordings by the "CO_2SMO Plus" monitor over a range of 2-60 cmH_2O were within ± 2% of those displayed by an electronic manometer (Digitron – pressure manometer P200UL). Prior to use the accuracy of individual sensors was checked by using a calibrated syringe (Hans Rudolf Inc.– calibrated volume syringe) to deliver a 10 ml (neonatal) or 100 ml (paediatric/adult) sensor signal. The least squares algorithms employed by the "CO_2SMO Plus" to calculate C_{rs} and R_{rs} were checked against linear regression of raw

data points and found to be accurate to within 5%. In addition C_{rs} measurements were checked against known values of C_{rs} on a Manley neonatal lung simulator and measurement errors were found to be < 5% for the full clinical range of respiratory rates and peak inspiratory pressures.

Written informed consent was obtained from the parents of all children included in the study. Subjects were monitored continuously for at least 5 consecutive hours, during which time nursing and medical procedures such as physiotherapy, postural changes and tracheal suction were performed as usual. These long periods of continuous measurement provided the opportunity to investigate the occurrence, magnitude and variability of tracheal tube leaks during a normal period of intensive care, as well as their consequences for the ventilated child. Only paralysed children were studied because those making spontaneous ventilatory efforts would have required additional oesophageal manometry to differentiate between chest wall and lung mechanics, which was not available from the "CO_2SMO Plus" (14). All patients were paralysed and sedated with pain relief according to unit protocols using standard doses of vecuronium (2-4 mcg/kg/min), morphine (10-14mcg/kg/hr) and midazolam (1-6 mcg/kg/hr).

Expired tidal volume was integrated from expiratory flow, while compliance and resistance were automatically computed by the "CO_2SMO Plus" throughout the breath cycle using the least squares regression method (14). Inspiratory and expiratory resistance were calculated using data from the inspiratory and expiratory portion of the respiratory cycle respectively, whereas data throughout the whole breath was used to calculate compliance.

Inspired and expired tidal volumes, C_{rs}, and R_{rs} were continuously recorded and breath by breath values were averaged for each minute of recording. Tracheal tube leak was neither automatically calculated nor displayed by the "CO_2SMO Plus" or Analysis Plus software. For the purposes of this study, it was computed from online recordings as the difference between each minute's averaged values of inspired and expired tidal volume using the equation:

$$\% \text{ leak} = \frac{(V_{TI} - V_{TE})}{V_{TI}} \times 100$$

Changes in tidal volume, resistance and compliance were related to simultaneous changes in leak during the monitoring period.

Results

Of the 75 paralysed ventilated children studied, 61 had pressure controlled ventilation: median age 0.25 years (0.02 to 12.8 years) and weight 4.3 kg (2 to 87 kg) and 14 had volume controlled ventilation: median age 4 years (0.02 to 10.5 years) and weight 15.8 kg (3 to 30 kg). 4 children in each group had a cuffed tracheal tube: median age 8 years (4 - 16 yrs) weight 22 kg (13.9 - 87 kg), all of whom had tube leaks <5%. Tracheal tube sizes ranged between 3.0 and 7.5mm. Over half of the infants (43/75) were studied following corrective cardiac surgery for congenital defects: median age 8 weeks (3days - 16 yrs). The remaining children were studied in the paediatric intensive care unit following admission for a variety of reasons including head injury, gastric transposition surgery, respiratory or multi-organ failure: median age 22 months (1 week to 16 yrs). Ten children (13%) had a mean tracheal tube leak greater than 20% (21.9 - 65.1%), median age 0.12 years (0.02 - 1.3 yrs) and weight 2.95 kg (2.6 - 9.8 kg). In the latter group, there were particularly wide within and between-subject fluctuations with respect to the magnitude of leak, V_{TE}, C_{rs} and R_{rs} during the monitoring period.

Figure 1 summarises data recorded over several hours in two infants in whom ventilatory settings remained constant during the monitoring period. The relationship between both inspired and expired tidal volume and changes in percentage of leak are displayed. In the first example from a 16 month old male infant on Servo 300 pressure pre-set ventilation (figure 1a) the leak varied between 10% and 70% over a six hour period and was accompanied by a 30% increase in inspired tidal volume and a 60% reduction in expired volume. By contrast, but as expected, during volume controlled ventilation (also via a Servo 300 ventilator), (figure 1b) inspired volume remained relatively constant in a 5 day old (2.88 kg) infant over 7 hours of monitoring. This was however, accompanied by a marked reduction in expired volume as the leak increased, with expired tidal volume halving when leak was maximal. In this infant there was a strong negative correlation ($r^2 = 0.93$) between V_{TE} and leak. There was also a strong positive correlation between leak and C_{rs} ($r^2 = 0.68$) and inspiratory and expiratory resistance ($r^2 > 0.92$) (Figures 2a, 2b, 2c, 2d). It can be seen that, in the presence of a large leak, values of C_{rs} and R_{rs} in this neonate, were distorted far beyond the range previously reported in ventilated newborns i.e. 0.2-1 $ml.cmH_2O^{-1}.kg^{-1}$ and 70 -150 $cmH_2O.l^{-1}.s$ (5,14-17).

The influence of the large tracheal tube leak on the shape of flow volume and pressure volume curves is illustrated in figure 3 which shows data from a 7 week old (2.6 kg) baby who was on pressure pre-set ventilation (Bear Cub BP2001), both before and after the tracheal tube was changed from a size 3.0mm to a size 4.0mm. Data were collected for 7 hours prior to and 5 hours after tube change and the results are summarised in figure 4. Clinical status was stable and ventilator settings not altered during this period suggesting that the observed changes in tidal volume, compliance and resistance were attributable to the change of tracheal tube.

It can be seen that the reduction in tracheal tube leak from over 80% to an average of 16% was accompanied by a marked reduction in both the magnitude and variability of compliance (Figure 4b) and resistance (Figure 4c and 4d). While some of the reduction in leak can be attributed to the insertion of a larger tracheal tube, (18)this cannot account for the magnitude of change observed or the reduction in variability. In addition, even within the smaller range of leak that occurred after the tracheal tube had been changed (11 - 23%) there was still a significant correlation ($r^2 = 0.84$) between calculated values of resistance and magnitude of leak (Figure 4c).

In an attempt to identify the magnitude of leak that would preclude accurate measurements, the median and inter-quartile range of all values of weight corrected compliance for each of the 75 children studied were plotted against the mean leak in that child during the measurement period (Figure 5). Tracheal tube leaks greater than 20% were associated with a marked rise in both the absolute values and the variability of weight corrected compliance. A similar pattern was obtained when resistance data were plotted in the same way.

Discussion

These results confirm in vivo those of previous in vitro lung model studies which show that compliance and resistance values are overestimated in the presence of tracheal tube leak (11-13,19). Interpretation of these findings is dependent both on the ability of the monitoring equipment to record volume and pressure changes accurately and the absence of various confounding issues such as changes in ventilatory management and/or clinical status that can occur when undertaking such studies on the ICU.

Many of the potential confounders were avoided by limiting measurements to paralysed fully ventilated children in whom ventilatory settings remained unchanged during the period of monitoring. Since unit policy was to maintain a constant paralysis rather than intermittently reducing doses, the observations reported in this paper should not have been confounded by any changes in mechanics associated with waxing or waning of the muscle relaxant agent used.

Extensive bench testing to validate the accuracy of the "CO_2SMO Plus" sensors suggested that the observed discrepancies between V_{TI} and V_{TE} were indeed due to the presence of a tracheal tube leak rather than any equipment or software errors. The importance of assessing the accuracy of both equipment and software used to assess respiratory function in infants has been stressed in several recent publications (20-24)

Magnitude of leak is conventionally assessed as the percentage difference between V_{TI} and V_{TE} and as such there will obviously be a strong negative relationship between percent leak and V_{TE}. However the clinical significance of a calculated leak will to some extent depend on the type of ventilatory management.

During pressure controlled ventilation, leak magnitude reflects both overestimation of V_{TI}, much of which having passed through the flow-meter will leak out around the tube before entering the child's lungs, and the reduction in V_{TE}. In turn the latter will primarily reflect a reduction in the actual delivered volume although in the presence of a very loose fitting tube or any secretions within the tube some expired air may shunt through the leak pathway without passing through the flow-meter thereby underestimating true expired volume. During pressure controlled ventilation there will be some compensatory increase in delivered volume as the ventilator attempts to maintain a constant peak inspired pressure whereas this will be far less marked during volume controlled ventilation as shown in figure 1b. Consequently, the same magnitude of leak is likely to reflect a greater reduction in delivered tidal volume during volume

than pressure controlled ventilation (25). Theoretically during pressure controlled ventilation in the presence of a very large leak and/or a low bias flow the time to reach peak inflation pressure could be prolonged thereby rendering inspired volume artificially larger relative to expired volume. In such circumstances the clinical significance of the observed leak would only be obviated if expired volume remained constant. Such an occurrence never occurred in this study, the magnitude of the leak always being primarily dependent on the reduction of the expired tidal volume rather than overestimation of inspired tidal volume.

Thus, changes in tracheal tube leak do not simply confound the calculation of respiratory function parameters, but may be associated with significant clinical consequences if there is inconsistent ventilatory delivery. For example, inadequate ventilation may occur if the leak increases following a change in patient position, whereas, unless appropriate modifications of ventilator settings are made, excessive ventilation with the attendant risks of volutrauma or barotrauma can occur if the leak suddenly decreases. This study has illustrated the magnitude and variability of leak during routine intensive care. In general, the larger the mean leak, the greater the variability both in delivered tidal volume and in the values calculated for compliance and resistance. In the presence of tracheal tube leak, apparent changes in compliance or resistance may not reflect real clinical changes, but simply a change in the magnitude of leak due, for example, to physiotherapy or alterations in head, neck or body position. Whether such changes have a beneficial or deleterious clinical effect will depend on the adequacy of ventilation prior to the intervention and the magnitude of leak change. Confusingly, the clinician will see an apparent "improvement" in compliance but "deterioration" in resistance as the leak gets larger, since both are increasingly overestimated as leak increases, whereas the opposite is true if a reduction in tracheal tube leak occurs. Clinical decisions based on these data would be unsound and any attempt to optimise ventilatory management in order to achieve optimal blood gases while minimising the risk of lung injury is not possible in the presence of such intra-subject variability.

Clinical interpretations may be further confounded by the fact that changes in the clinical status of the child may also cause changes in leak magnitude. Thus, a reduction in respiratory compliance may result in an increased leak, which could in turn exacerbate further clinical deterioration due to inadequate ventilatory delivery. Conversely, any

improvement in respiratory compliance could lessen the leak and further increase ventilation delivery, potentially leading to over-inflation. This is in some ways analogous to the situation that seemed to occur during the early trials of surfactant, when failure to adjust ventilator settings following surfactant therapy led to over-inflation of the lungs thereby masking any improvement in dynamic lung compliance due to the therapeutic intervention (14,16,17,26,27)

Establishing how much leak is acceptable in a ventilated child depends very much on the clinical status of the child. The results from this study suggest that attempts to optimise ventilatory management in the clinical situation are impossible in the presence of tube leaks greater than 15 - 20%. For satisfactory clinical management and to avoid exposure of the child to sudden changes in tidal volume delivery and gas exchange, maximum leak should not exceed 20% and variability of leak should be < 10%.

Whereas measurements of C_{rs} appear to be more robust, any attempt to use resistance as an outcome variable to evaluate therapeutic interventions such as steroid or bronchodilator therapy would require negligible leak throughout the entire period of study. Such a condition may not be attainable unless a cuffed tube is in situ (1).

Sly et al suggested that the use of the expiratory portion of each breath to calculate respiratory mechanics might reduce the confounding effect of leak but cautioned that this method has not yet been thoroughly validated (14). A lung model study by Kondo et al suggested that resistance could be reported reliably provided only the expiratory portion of the breath was used, when airway pressure was lower and hence leak smaller (12). This is in contrast to the results from this in vivo study, which found that both inspiratory and expiratory resistance were overestimated and unreliable in the presence of tracheal tube leak greater than 10%. The discrepancy in results between in vivo and in vitro studies may be explained by the difficulty of designing lung models to approximate the clinical situation where the presence of lung disease may exaggerate the effect of leak, and indicates that results from in-vitro studies should be interpreted with caution.

In addition, in the presence of a large leak, changes in time constant and introduction of phase lags between flow and pressure signals are likely to invalidate the data collected and the algorithms applied, irrespective of phase of the respiratory cycle. When interpreting measurements of resistance in ventilated infants, it should be noted that, in addition to the presence of any leak, measurements may be confounded by the resistance of the tracheal tube which may represent the largest component of the total resistance,

especially in neonates with small tubes (18,28). In addition, variations in calculated resistance may occur according to both the equipment and algorithms used (29) and the age and size of the child. Whilst there are limited data available for 'healthy' ventilated children, a recent study by Lanteri et al in 51 anaesthetised, intubated children ranging from 3 week to 15 years, showed that resistance fell from around 130 to 15 $cmH_2O.l^{-1}.s$ during this period of growth and development (30).

The results from the current study suggest that a minimal leak (5-10%) is essential if parameters of respiratory function are to be used as objective outcome measures, particularly if such measures are required to detect within-subject changes in response to therapeutic interventions. Unfortunately significant leaks are not always audible or clinically obvious and their magnitude is not always accurately displayed on the ventilator or monitoring equipment, if at all. Indeed, no automatic display of the magnitude of leak was available when using the "CO_2SMO Plus", although it was possible to calculate these values for the purposes of this study. Leaks present in the circuit between the ventilator and tracheal tube would not have been recorded by the "CO_2SMO Plus" flow sensor and so should not have introduced error into measurements of V_T or C_{rs} and R_{rs} made at the airway opening. However, such leaks would affect parameters displayed on ventilators which measure flow at some distance from the airway opening and could contribute to known errors associated with these measurements (31).

Tracheal tube leaks would be less clinically relevant if cuffed tracheal tubes were more widely used in the paediatric ICU. Although an increasing number of centres in America and Europe are now using cuffed tubes, anxieties about the possibility of tracheal damage from cuffed tracheal tubes remain, despite the lack of firm evidence to support these concerns. In contrast there are studies that suggest that cuffed tubes are safe in children (32-35). Deakers et al. found no association between cuffed tracheal tube intubation in children and post extubation stridor or long term tracheal sequelae (32). They emphasised that infants with decreased compliance may require high PEEP and relatively high PIP to maintain adequate tidal volumes. In such patients a cuffed tracheal tube will provide optimal and consistent levels of ventilation and PEEP, whereas a significant tracheal tube leak may hamper these two goals of ventilation. The use of a cuffed tube however, normally requires a smaller internal diameter and hence higher resistance, which may limit their application in neonates.

Conclusion

The magnitude of tracheal tube leak is not stable in individual children and in general, the larger the leak, the greater the variability of respiratory function measurements obtained. Leaks larger than 20% result in gross over-estimations of compliance and resistance irrespective of mode of ventilation. Even when leak is less than 20%, a significant correlation between its magnitude and measures of respiratory mechanics remains. Consequently, measures of respiratory function cannot be used to optimise ventilatory management in the presence of moderate to large leaks and it may become clinically difficult to ensure consistent and adequate ventilation. If changes in mechanics are to be used as reliable outcome measures in ventilated children it is probably advisable to ensure that the leak is less than 5-10% and the variability is small.
The magnitude of leak needs to be accurately displayed on all ventilatory equipment to facilitate appropriate clinical decisions. Further work is required to establish the significance of clinical changes (including blood gases) which accompany any change in tracheal tube leak in specific groups of ventilated children.

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Figure legends:

Figure 1: The relationship between inspired and expired tidal volume and percentage leak in a) a 16 month old infant on pressure pre-set ventilation (Servo 300) and b) a 5 day old infant on volume pre-set ventilation (Servo 300).

Tracheal tube leak is calculated from the difference between inspiratory (V_{TI}) and expiratory (V_{TE}) tidal volume. Each data point represents the mean value from one minute of recording.

Figure 2: The relationship between tracheal tube leak and a) tidal volume, b) compliance, c) inspiratory resistance and d) expiratory resistance in a 5 day old infant.

Each data point represents the mean value from one minute of recording.

Figure 3: Flow/volume and pressure/volume loops (a) before and (b) after tube change from 3.0mm to 4.0mm in a 7 week old infant.

Loops generated from a 7 week old infant receiving pressure controlled ventilation.

Figure 4: Influence of tracheal tube change from 3.0mm to 4.0mm on a) tidal volume, b) compliance, c) inspiratory resistance and d) expiratory resistance in a 7 week old infant.

Each data point represents the mean value from one minute of recording from a 7 week old infant receiving pressure controlled ventilation (Bear Cub BP2001). Effective expired tidal volume was three times higher following tube change and reduction of leak. Note the gross overestimation and greater variability of calculated compliance and resistance in the presence of a large leak.

Figure 5: Median and interquartile range of compliance at different tracheal tube leaks

Each data point represents the data set from one child over at least 5 hours of monitoring. With leaks greater than 20% there is a significant rise in the calculated values and variability of compliance.

Figure 1.

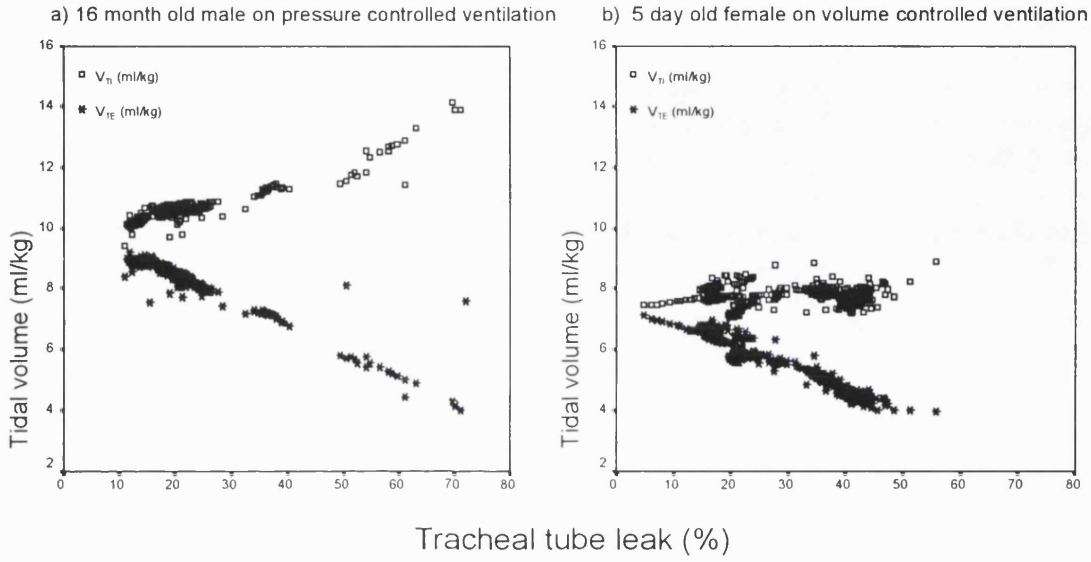

Figure 2

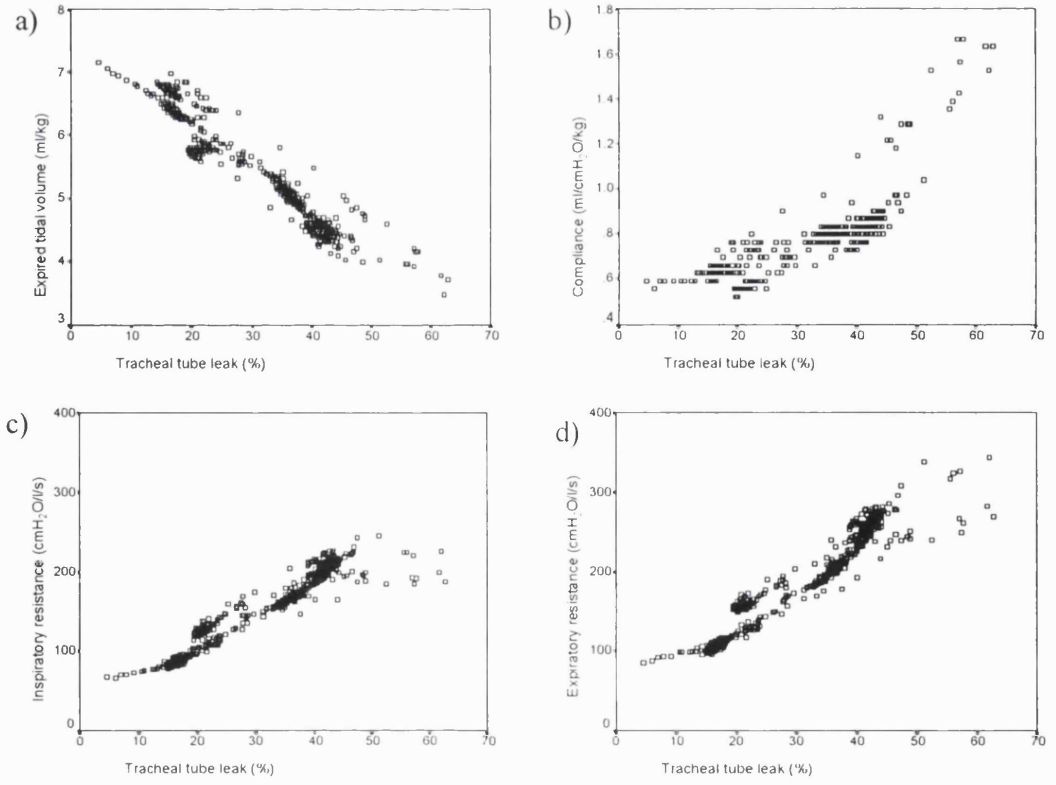

Figure 3.

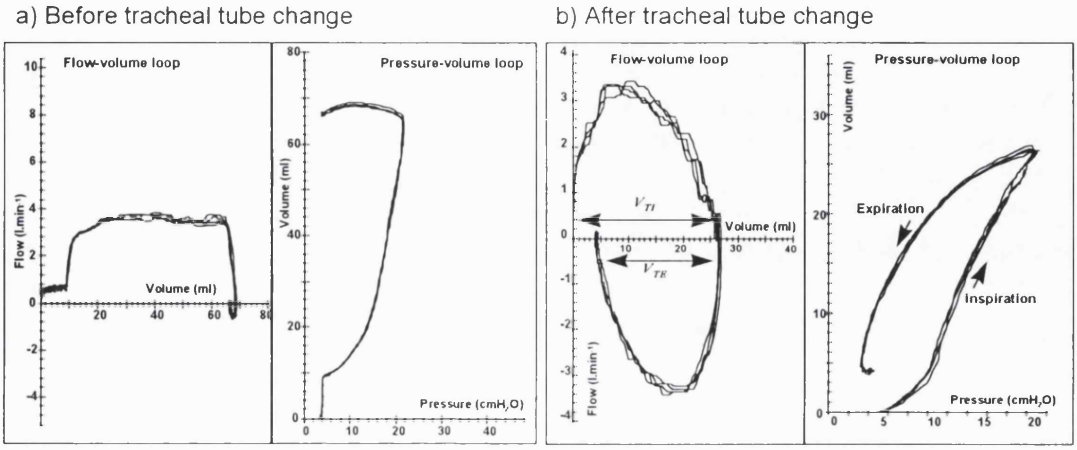

Figure 4

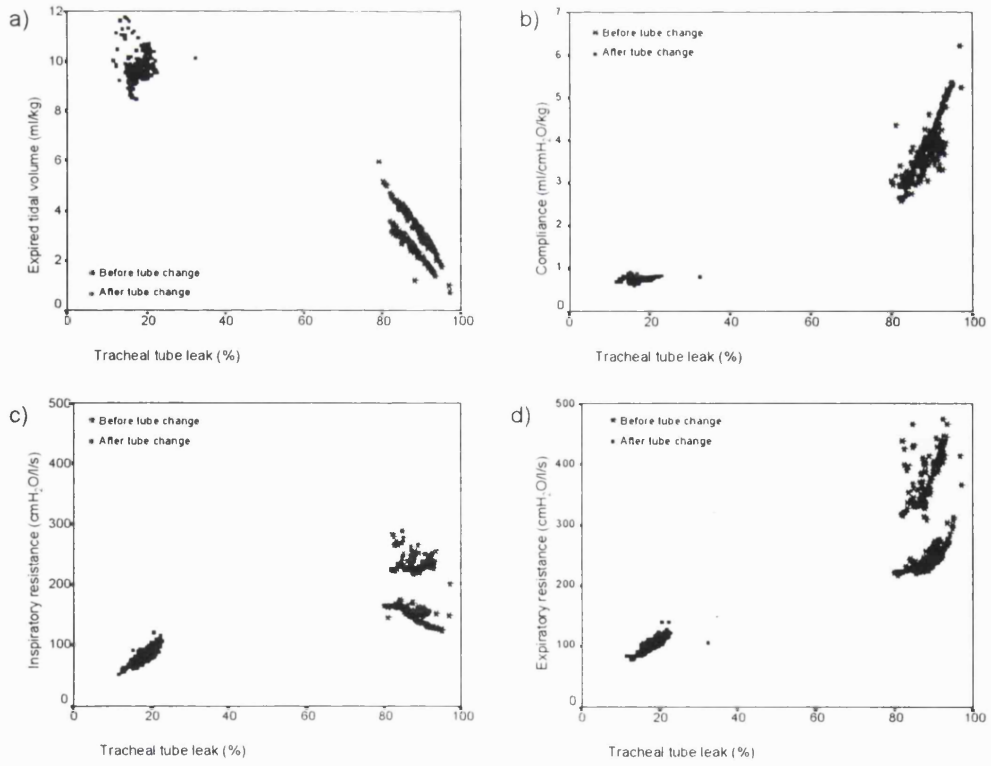

Figure 5.

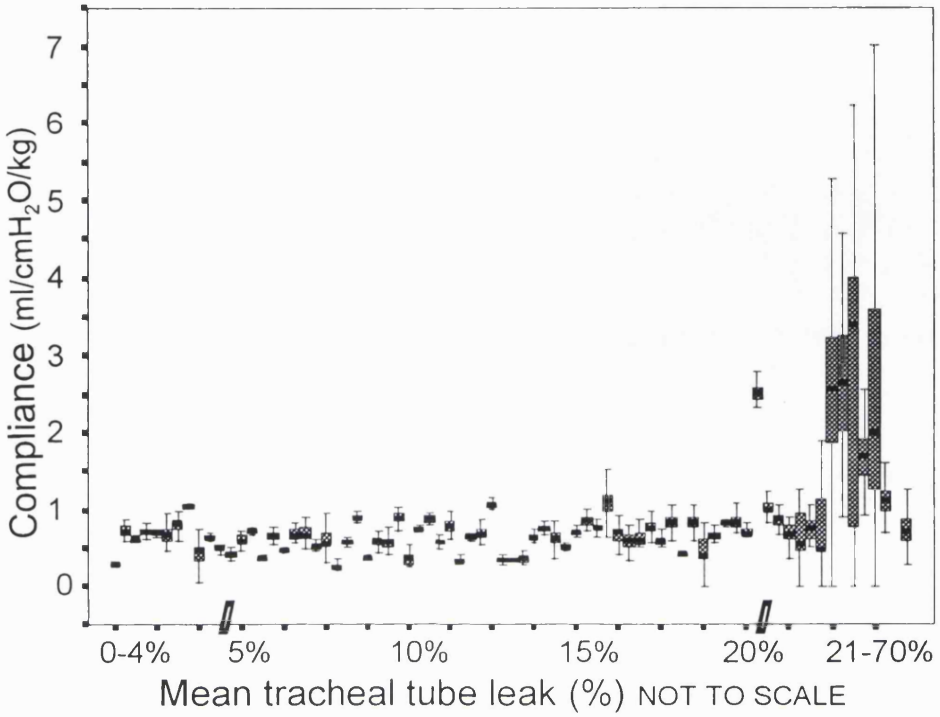

Table 1: Volume accuracy of the flow sensors

	Mean % Error (SD) [1]		% Difference V_{TI} -V_{TE}
	V_{TI}	V_{TE}	[Mean (SD)] [2]
Neonatal sensor (no tracheal tube)	0.5 (2.3)	0.5 (3.2)	0.01 (2.0)
Neonatal sensor with tracheal tube (sizes 3 - 6.5)	2.2 (1.6)	0.8 (2.9)	1.3 (1.9)
Paediatric sensor (no tracheal tube)	1.2 (1.2)	-3.2 (1.9)	4.4 (1.4)
Paediatric sensor with tracheal tube (sizes 3 - 6.5)	0.9 (2.1)	1.1 (4.0)	-0.3 (4.4)
Adult sensor (no tracheal tube)	3.3 (2.8)	-0.6 (1.9)	3.7 (2.1)
Adult sensor with tracheal tube (sizes 3.5 - 6.5)	3.2 (1.9)	0.5 (2.3)	2.5 (2.1)

Footnote to Table 1.

[1] Mean percentage error calculated as [100 x (measured - applied) / applied]

[2] Mean difference between inspired and expired volume calculated as:

$$[100 \times (V_{TI} - V_{TE}) / V_{TI}]$$

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10. Appendix

10.1 Parents Information Sheet

Information Sheet

The effect of dynamic respiratory physiotherapy and routine airway clearance techniques on respiratory function in the paediatric intensive care

We would like to ask your permission to include your child in this project

Aim of the study.

Almost all children who are ventilated in the intensive care unit will have chest physiotherapy and routine suction to clear secretions from the airways.
The aim of this project is to investigate exactly what effect the chest physiotherapy treatments have on lung function and whether these treatments are more effective than the suction that is done by nurses.

Why is the study being done?

We do not know exactly what effect chest physiotherapy has on the lungs. We also do not know whether these treatments are any better than the routine suction that is done by the nurse.
This is because suitable equipment has not been available until recently to measure lung function in the intensive care unit. Now that the equipment is available, it will help us to evaluate the treatment we are providing in an objective way.

How is the study to be done?

A very small monitor will be attached to the ventilator tubing which will measure how much air is going to the lungs from the ventilator. This monitor can be left in place for long periods of time without causing any problems or interfering with routine treatment in any way. The monitor will be attached for most of the day on which the study will take place and will automatically measure what is happening to the lungs before and after each treatment.
In the morning your child will be suctioned either by the nurse or by the physiotherapist. In the afternoon, the your child will receive whichever treatment they did not have in the morning. If your child needs further suction or treatment in between, these will be performed as normal by the nursing or physiotherapy staff. The way in which your child is managed on the intensive care unit will not be affected by this study.
Your child will already have an arterial line in place. This is so that the nurse can draw small blood samples routinely to make sure the ventilator is giving your child the right amount of support.

Where possible, we will try and use the blood gas measurements that are taken by the nurse, but if not we will take an extra sample before and after the 2 treatments. In total this will be less than 1ml (half a teaspoon) of blood over the whole day and will not cause any distress or discomfort to your child.

One of the research team will spend most of the day near the bedside to make a note of what time the treatments occur, but if at any time you or your family wish to be alone with your child, we will be happy to accommodate your wishes.

Are there any risks and discomforts?

No risk or discomfort to your child is foreseen.

What are the potential benefits?

Although this study will have no direct benefits to your child, it will help us in the future to manage other children in the best possible way.

Who will have access to the research records?

Only the researchers and a representative of the research ethics committee will have access to the data collected during this study. This research has been approved by an independent research ethics committee who believe that it is of minimal risk to you.

Do I have to take part in this study?

If you decide now or at a later stage that you do not wish to participate in this research project, that is entirely your right and will not in any way change the way your child is treated.

Researcher who will have contact with the family

Eleanor Main: Phone: 0171 4059200 ext:5424
Rosemary Castle: Phone: 0171 4059200 ext:5454
Catherine Dunne: Phone: 0171 4059200 ext: 5144

Who do I speak to if problems arise?

If you have any complaints about the way in which this research project has been or is being conducted, please in the first instance discuss them with the researcher. If the problems are not resolved, or you wish to comment in any way, please contact the chairman of the Research Ethics Committee, by post via the Research and Development Office, Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, or if urgent, by telephone on 0171 242 9789. ext. 2620 and the committee administration will put you in contact with him.

10.2 Equipment validation

Table 10-1: Accuracy of volumes recorded by "CO_2SMO Plus" using the neonatal flow sensor.

Tracheal Tube Size	*Applied Volume*	** Recorded volume (mL)*		*CV (%)*		*% Error*	
	(mL)	V_{TI}	V_{TE}	V_{TI}	V_{TE}	V_{TI}	V_{TE}
No tracheal	2	1.97 (0.15)	1.95 (0.16)	7.6	8.2	-1.5 %	-2.5 %
tube	4	3.95 (0.13)	3.92 (0.13)	3.3	3.3	-1.3 %	-2.0 %
	6	5.96 (0.17)	5.93 (0.16)	2.9	2.7	-0.7 %	-1.2 %
	8	7.92 (0.19)	7.95 (0.23)	2.4	2.9	-1.0 %	-0.6 %
	10	9.94 (0.22)	9.91 (0.31)	2.2	3.1	-0.6 %	-0.9 %
	20	20.9 (0.65)	21.1 (0.68)	3.1	3.2	4.3 %	5.4 %
	40	39.4 (2.91)	39.2 (3.86)	7.4	9.8	-1.4 %	-2.0 %
	50	50.8 (1.07)	53.7 (3.67)	2.1	6.9	1.7 %	7.3 %
	60	58.9 (4.61)	58.5 (5.63)	7.8	9.6	-1.8 %	-2.5 %
	80	78.2 (6.62)	77.7 (7.63)	8.5	9.8	-2.2 %	-2.8 %
	100	102 (1.33)	102 (1.00)	1.3	1.0	1.8 %	2.1 %
	150	153 (1.85)	156 (5.93)	1.2	3.8	1.9 %	3.9 %
	200	206 (4.53)	203 (1.53)	2.2	0.8	3.2 %	1.4 %
	300	312 (5.68)	303 (1.40)	1.8	0.5	4.1 %	0.9 %
3.0 tracheal	20	20.9 (0.78)	21.3 (0.75)	3.7	3.5	4.3 %	6.6 %
tube	50	51.5 (3.58)	48.9 (2.06)	7.0	4.2	3.0 %	-2.3 %
	100	104 (4.42)	104 (2.76)	4.3	2.7	4.0 %	3.6 %
	150	153 (1.41)	150 (2.34)	0.9	1.6	2.0 %	-0.2 %
	200	200 (7.22)	198 (4.93)	3.6	2.5	0.2 %	-1.2 %
	300	303 (3.20)	290 (4.16)	1.1	1.4	1.1 %	-3.3 %
3.5 tracheal	20	21.0 (0.97)	21.2 (0.59)	4.6	2.8	5.2 %	5.9 %
tube	100	103 (1.80)	104 (2.24)	1.7	2.2	0.01%	-0.7 %
	300	305 (2.93)	302 (7.24)	1.0	2.4	1.6 %	0.8 %
4.5 tracheal tube	300	304 (4.63)	294 (3.44)	1.5	1.2	1.3 %	-2.1 %
6.5 tracheal	50	51.8 (2.35)	51.0 (1.45)	4.5	2.9	3.5 %	1.9 %
tube	150	155 (2.02)	153 (2.06)	1.3	1.3	3.2 %	2.2 %
	100	105 (2.46)	104 (2.67)	2.3	2.6	5.0%	4.0%
	200	203 (4.20)	202 (3.83)	2.1	1.9	1.4 %	1.1 %
	300	302 (11.1)	296 (6.32)	3.7	2.1	0.6 %	-1.4 %

Results are expressed as Mean (SD). Flow Between 0.75 - 28 L/min.

Table 10-2: Accuracy of volumes recorded by "CO_2SMO Plus" using the paediatric flow sensor.

Tracheal Tube Size	*Applied Volume (mL)*	*Recorded volume (mL)*		*CV*		*% Error*	
		V_{TI}	V_{TE}	V_{TI}	V_{TE}	V_{TI}	V_{TE}
No tracheal	40	40.3 (1.9)	39.4 (3.5)	4.7	8.9	0.7%	-1.5%
tube	50	51.1 (2.1)	48.4 (2.2)	4.1	4.6	2.1%	-3.2%
	60	61.2 (2.0)	59.1 (2.2)	3.2	3.7	2.0%	-1.6%
	80	80.7 (1.9)	77.0 (2.0)	2.4	2.6	0.9%	-3.7%
	100	102 (2.5)	97.2 (3.3)	2.4	3.4	2.5%	-2.9%
	150	155 (3.0)	150 (5.8)	1.9	3.9	3.1%	-0.2%
	200	200 (3.7)	191 (3.6)	1.9	1.9	-0.1%	-4.4%
	300	303 (3.6)	283 (20.2)	1.2	7.2	1.0%	-5.7%
	400	399 (10.6)	375 (6.0)	2.7	1.6	-0.3%	-6.3%
	500	500 (3.3)	485 (12.3)	0.7	2.5	0.1%	-3.0%
3.0 tracheal	40	39.7 (1.3)	43.9 (4.4)	3.4	9.9	-0.7%	9.8%
tube	50	53.1 (2.7)	51.2 (2.7)	5.0	5.3	6.1%	2.5%
	60	60.7 (1.4)	64.6 (1.8)	2.3	2.8	1.1%	7.6%
	80	81.7 (1.9)	87.3 (2.9)	2.3	3.3	2.1%	9.1%
	100	101 (2.1)	107 (2.7)	2.1	2.5	0.7%	7.3%
	150	148 (3.1)	151 (6.1)	2.1	4.0	-1.5%	0.9%
	200	197 (4.7)	200 (7.8)	2.4	3.9	-1.7%	0.1%
	300	300 (3.5)	307 (9.0)	1.2	2.9	0.1%	2.4%
	400	396 (5.8)	418 (11.0)	1.5	2.6	-1.1%	4.6%
	500	501 (4.1)	510 (8.7)	0.8	1.7	0.3%	0.2%
6.5 tracheal	50	52.4 (3.1)	49.4 (4.6)	5.9	9.4	4.7%	-1.2%
tube	80	80.5 (2.1)	76.6 (2.6)	2.6	3.4	0.7%	-4.3%
	100	101 (2.1)	97.7 (2.1)	2.1	2.2	1.3%	-2.3%
	150	154 (2.9)	149 (6.5)	1.9	4.4	2.9%	-0.8%
	200	203 (4.7)	194 (7.4)	2.3	3.8	1.5%	-3.1%
	300	297 (4.7)	304 (22.4)	1.6	7.4	-0.9%	1.2%
	400	400 (3.7)	390 (13.1)	0.9	3.4	0.1%	-2.6%
	500	498 (7.6)	486 (32.5)	1.5	6.7	-0.5%	-2.9%

Results expressed as mean (SD).

Table 10-3: Accuracy of volumes recorded by "CO_2SMO Plus" using the adult flow sensor.

Tracheal Tube Size	*Applied volume (mL)*	*Recorded volume (mL)*		*CV (%)*		*% Error*	
		V_{TI}	V_{TE}	V_{TI}	V_{TE}	V_{TI}	V_{TE}
No tracheal	40	39.4 (3.9)	38.9 (1.9)	9.8	4.8	-1.4%	-2.7%
tube	50	51.9 (2.0)	49.0 (1.6)	3.9	3.2	3.7%	-1.9%
	60	63.9 (6.1)	61.0 (5.3)	9.5	8.7	6.4%	1.6%
	80	80.3 (6.5)	78.9 (7.2)	8.1	9.1	0.4%	-1.4%
	100	102 (9.6)	97.5 (6.3)	9.4	6.5	2.2%	-2.5%
	150	155 (4.5)	147 (4.5)	2.9	3.1	3.5%	-1.8%
	200	207 (5.5)	203 (15.3)	2.7	7.6	3.5%	1.3%
	300	308 (6.1)	299 (17.4)	2.0	5.8	2.5%	-0.2%
	400	405 (16.5)	404 (18.5)	4.1	4.6	1.3%	1.1%
	500	525 (28.9)	489 (45.2)	5.5	9.3	5.0%	-2.2%
3.5 tracheal	50	54.3 (2.5)	51.3 (2.1)	4.5	4.1	8.7%	2.6%
tube	200	206 (4.8)	197 (4.4)	2.3	2.2	3.1%	-1.7%
	300	305 (6.1)	295 (11.1)	2.0	3.7	1.7%	-1.6%
	400	408 (12.1)	395 (11.2)	3.0	2.8	2.1%	-1.2%
	500	506 (23.2)	492 (15.4)	4.6	3.1	1.1%	-1.6%
6.5 tracheal	50	53.5 (3.1)	52.1 (2.7)	5.9	5.2	7.1%	4.3%
tube	150	156 (3.9)	151 (6.6)	2.5	4.4	3.8%	0.5%
	200	211 (5.6))	202 (7.3)	2.7	3.6	5.6%	1.2%
	300	308 (23.5)	298 (10.9)	7.6	3.6	2.6%	-0.5%
	400	412 (7.6)	406 (9.4)	1.8	2.3	3.1%	1.6%
	500	508 (36.3)	522 (44.5)	7.2	8.5	1.5%	4.4%

**Results expressed as mean (SD). Volumes < 40mL were not accurately measured with the adult flow sensor.*

Table 10-4: Pressure recordings by "CO_2SMO Plus" compared to Digitron

	Manometer pressure	*Recorded pressure (kPa)*	*CV (%)*	*% error*
Neonatal	59.8	61.0 (0.03)	0.06	-2.07
sensor	38.3	39.0 (0.06)	0.14	-1.90
	24.4	24.8 (0.06)	0.24	-1.79
	15.5	15.7 (0.02)	0.11	-1.53
	9.73	9.72 (0.03)	0.32	0.12
	6.03	6.02 (0.02)	0.41	0.14
	3.63	3.61 (0.03)	0.78	0.61
	2.27	2.20 (0.01)	0.42	3.06
Paediatric	58.5	59.6 (0.65)	1.09	-0.02
sensor	55.2	56.5 (0.96)	1.70	-0.02
	34.9	35.1 (0.23)	0.65	-0.01
	32.2	32.6 (0.53)	1.64	-0.01
	21.2	21.3 (0.02)	0.11	-0.01
	16.0	16.2 (0.05)	0.30	-0.01
	11.7	12.0 (0.02)	0.17	-0.03
	9.00	8.85 (0.11)	1.20	0.02
	6.74	6.75 (0.05)	0.76	0.00
adult	51.5	52.0 (0.05)	0.09	-0.01
sensor	28.6	29.0 (0.05)	0.18	-0.01
	63.4	63.7 (0.04)	0.06	-0.01
	18.5	19.1 (0.03)	0.17	-0.03
	10.5	10.3 (0.08)	0.74	0.02
	11.5	11.7 (0.03)	0.22	-0.02
	12.0	12.2 (0.04)	0.35	-0.02
	5.20	5.35 (0.05)	0.99	-0.03

10.2.1.1 Within subject variability

Table 10-5: Within subject variability of parameters in 33 individuals over a 30 minute period

Parameter	*mean CV*
Tube leak (%)	1.6%
V_{TE} (mL/kg)	2.2%
Rrs (cmH_2O/L/sec)	4.7%
Crs (mL/cmH_2O/kg)	3.1%
VCO_2 (mL/min/kg)	3.8%
$ETCO_2$	1.3%
$PeCO_2$	3.5%

Parameter	*mean CV*
Resp. rate	1.8%
PIP	1.8%
PEEP	1.6%
MAP	1.1%
PEF	2.7%
t_I	1.0%
t_E	1.9%

10.3 Study protocol

1. In the first instance only fully ventilated paralysed and sedated patients will be included.
2. Written consent will be sought from parents of suitable children.
3. The patient will be assessed for airway leak (>20%). In the presence of a significant leak, the senior registrar or consultant will be informed. If the endotracheal tube is changed to reduce the leak, patients will be included in the study.
4. Only patients with arterial lines in situ will be included.
5. The ventilator connections should be checked to be compatible with the "CO_2SMO Plus" and adapted if necessary.
6. The physiotherapist and nurses involved will be blind to the trend data so that treatment techniques are not adjusted on the basis of the recordings.
7. Name, address and demographic details of the child will be recorded but coded so that electronic data storage will not identifiable. Clinical and ventilation details and clinical interventions and events will be recorded.
8. A bedside information sheet will be prepared to explain the measurements being recorded. This will be for the benefit of nursing staff and parents if required.
9. All measurements will be performed in supine even if treatments involved postural drainage for the duration of treatment.
10. Water will be emptied from the ventilator tubing.
11. 30 minutes prior to treatment, patients will be connected to the "CO_2SMO Plus" and recordings will commence. The "CO_2SMO Plus" will be connected for at least one 15 minute interval (but preferably longer in divisions of 15 minute periods) before the nursing or physiotherapy intervention is performed. Trend data (averaging every minute) on various respiratory parameters will be collected. The maximal time for trend data to be collected following any intervention will be 4 hours. (16 fifteen minute intervals).
12. Five minutes after connection, a five minute buffer of flow/volume loops, pressure/volume loops, and breath wave-form data will be collected.
13. An arterial blood will be taken in the 10 minutes immediately preceding the nursing or physiotherapy intervention. The exact time of sampling will be recorded for the "real time" deadspace calculations to be performed. In addition the last available

blood gas prior to recording will be collected for assessing general stability of this parameter in the individual patient.

14. Immediately prior to the nursing or physiotherapy treatment, data recording will cease and the "CO_2SMO Plus" will be disconnected. This will allow the flow/volume loops, pressure/volume loops, and breath wave-forms from the five minute period preceding the intervention to be downloaded.
15. During the physiotherapy or nursing intervention, detailed recording of the intervention will be taken on the form provided.
16. Water will be removed from the ventilator tubing prior to reconnection.
17. The patient will be settled in the supine position following treatment.
18. As soon as the patient has finished having treatment and is settled (no further handling) the "CO_2SMO Plus" will be reconnected and recording will recommence.
19. Five minutes after connection, a five minute buffer of flow/volume loops, pressure/volume loops, and breath wave-form data will be collected.
20. Trend data will continue to be collected for at least 30 minutes following treatment but where possible, trend data will be collected continuously between interventions for the purpose of:
    - Assessing the effect of any clinical interventions between treatments
    - Assessing the length of effect of the previous intervention
    - Assessing the general respiratory stability of the individual.
    - Assessing normal variability during the day for that individual.
    - Calculating physiological deadspace measurements when routine arterial blood gas measurements are taken.
21. Ideally, no nursing cares, suction, ventilator changes, chest radiographs, position changes or any examinations or handling should occur during the 30 minute data collection periods immediately prior to or following treatment. The exception will obviously be in the event of urgent clinical need in which case the data will have to be discarded. Where possible minimal interventions should occur in the hour preceding and following interventions so that arterial blood gases are reflective of clinical status rather than extraneous factors.
22. At least 30 minutes and less than one hour after treatment another "real time" arterial blood gas will be collected and deadspace calculations will be performed. In

addition the next available blood gas will be collected for assessing general stability of this parameter in the individual patient.

23. If suction is required during the 4 hour interval following treatments, then it will be documented. Any other clinical interventions for example feeds, nursing cares, position changes, chest radiographs, changes in ventilation during the four hour period following either intervention will be recorded in detail and taken into account during analysis of the data. The research team will remain present to document these interventions. The trend data collected around these interventions will be analysed.
24. Only experienced nursing and physiotherapy staff will perform the interventions. It is possible that only 3-4 physiotherapists will do the treatments while several more may do the nursing interventions.