A comparison of five airway clearance techniques in the treatment of people with cystic fibrosis

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Abstract

A comparison of five airway clearance techniques in the treatment of people with cystic fibrosis

The evidence in the literature today indicates that there are neither statistically nor clinically important differences in effectiveness among the airway clearance techniques of the active cycle of breathing techniques, autogenic drainage, cornet, flutter or positive expiratory pressure in the short term. There is little evidence of the effects of the different regimens in the long term. Excluding autogenic drainage, all regimens now include the forced expiratory manoeuvre of 'huffing' and this may be one of the most effective components of airway clearance.

This study was to evaluate the long term effects, over one year, of the five airway clearance techniques in adults with cystic fibrosis. Seventy-five subjects entered the prospective, randomised controlled trial. The primary outcome measure was forced expiratory volume in one second (FEV_1), the null hypothesis being that there are no differences among the regimens. Secondary outcome measures included other measures of lung function, body mass index, exercise capacity (modified shuttle test), health related quality of life (Short Form-36 and Chronic Respiratory Questionnaire) and treatment with intravenous antibiotics.

Using intention to treat, data was available on 65 subjects at the end of the study period. The mixed model analysis of variance was used to analyse the data. There were no statistically significant differences among the regimens in the primary outcome measurement of FEV_1 ($p=0.35$), but there was a significant overall deterioration over time ($p=0.02$).

There were no statistically significant differences among the regimens in the secondary outcome measurements of forced vital capacity (FVC), maximal expiratory flow at 25% of forced vital capacity (MEF_{25}), residual volume as a percent of total lung capacity (RV%TLC), body mass index (BMI), exercise capacity, quality of life or use of intravenous antibiotics. In different countries either one or several airway clearance regimens are practised. This thesis provides evidence in support of current practices.

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Abbreviations

%	Percent
<	Less than
>	Greater than
ACBT	Active cycle of breathing techniques
AD	Autogenic drainage
BMI	Body mass index
bpm	Beats per minute
CCI	Cough clearability index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CRQ	Chronic Respiratory Disease Questionnaire
df	Degrees of freedom
e.g.	For example
EPP	Equal pressure point
F	Frequency
FEF_{25-75}	Forced expiratory flow at 25 – 75% of forced vital capacity
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
H_2O	Water
Hg	Mercury
Hz	Hertz
kg	Kilograms
LED	Light emitting diode
m	Metres
MCI	Mucociliary clearability index
MEF_{25}	Maximal expiratory flow at 25% of forced vital capacity

MEF_{50}	Maximal expiratory flow at 50% of forced vital capacity
MID	Minimally important difference
mm	Millimetres
mmol	Millimole
MS	Mean of squares
MST	Modified shuttle test
Mu	Mucus
N	Number
NS	Not significant
PEF	Peak expiratory flow
PEP	Positive expiratory pressure
PIF	Peak inspiratory flow
PT	Physiotherapy / Physical Therapy
RIM	Resistive inspiratory manoeuvres
RV	Residual volume
RV%TLC	Residual volume as a percent of total lung capacity
SD	Standard deviation
SEM	Standard error of the mean
SF-36	Short Form-36 questionnaire
SpO_2	Oxygen saturation
SS	Sum of squares
TIRE	Test of incremental respiratory endurance
TLC	Total lung capacity
TV	Tidal volume
UK	United Kingdom
USA	United States of America
V	Variance

$\dot{V}$	Flow
VC	Vital capacity
α	Alpha
β	Beta

Publications by the Author that formed the background to this thesis

The work listed here highlighted the need for an evidence based study to identify which technique or techniques should be recommended for people with cystic fibrosis in the long term.

1 Peer reviewed papers

Pryor JA 2004 Physical therapy for adults with bronchiectasis *Clinical Pulmonary Medicine* 11(4): 201 - 209

Pryor JA 1999 Physiotherapy for airway clearance in adults *European Respiratory Journal* 14: 1418 - 1424

Carr L, Smith RE, **Pryor JA**, Partridge C 1996 Cystic fibrosis patients' views and beliefs about chest clearance and exercise - a pilot study *Physiotherapy* 82: 621 - 627

Pryor J 1996 Active cycle of breathing techniques *Israel Journal of Medical Sciences* 32: S14-S15

Carr L, **Pryor JA**, Hodson ME 1995 Self chest clapping - patients' views and the effects on oxygen saturation *Physiotherapy* 81: 753-757

Pryor JA, Webber BA, Hodson ME, Warner JO 1994 The Flutter VRP1 as an adjunct to chest physiotherapy in cystic fibrosis *Respiratory Medicine* 88: 677-681

Steven MH, **Pryor JA**, Webber BA, Hodson ME 1992 Physiotherapy versus cough alone in the treatment of cystic fibrosis *The New Zealand Journal of Physiotherapy* 20: 31-37

Pryor JA, Webber BA, Hodson ME 1990 Effect of chest physiotherapy on oxygen saturation in patients with cystic fibrosis *Thorax* 45: 77

Partridge C, **Pryor J**, Webber B 1989 Characteristics of the forced expiration technique *Physiotherapy* 75: 193-194

Pryor JA, Parker RA, Webber BA 1981 A comparison of mechanical and manual percussion as adjuncts to postural drainage in the treatment of cystic fibrosis in adolescents and adults *Physiotherapy* 67: 140-141

Pryor JA, Webber BA 1979 An evaluation of the forced expiration technique as an adjunct to postural drainage *Physiotherapy* 65: 304-307

Pryor JA, Webber BA, Hodson ME, Batten JC 1979 Evaluation of the forced expiration technique as an adjunct to postural drainage in treatment of cystic fibrosis *British Medical Journal* 2: 417-418

2. Books, Chapters, Theses

Pryor JA, Main E, Agent P, Bradley JM 2005 Physiotherapy In: *Progress in Respiratory Research: Cystic Fibrosis* Bolliger CT (Series Editor). Bush A (Volume Editor) Karger, Basel (Invited lead author)

Pryor JA, Webber BA 2002 Physiotherapy techniques. In: **Pryor JA**. Prasad SA (eds) *Physiotherapy for respiratory and cardiac problems - adults and children* (3rd edn) Churchill Livingstone, Edinburgh

Pryor JA, Webber BA 2000 Physiotherapy in cystic fibrosis. In: Hodson ME, Geddes DM (eds) Cystic *Fibrosis* (2nd edn) Arnold, London

Webber BA, **Pryor JA** 1998 Physiotherapy techniques. In: **Pryor JA**, Webber BA (eds) *Physiotherapy for respiratory and cardiac problems* (2nd edn) Churchill Livingstone, Edinburgh

Webber BA, **Pryor JA** 1998 Bronchiectasis, primary ciliary dyskinesia and cystic fibrosis. In: **Pryor JA**, Webber BA (eds) *Physiotherapy for respiratory and cardiac problems* (2nd edn) Churchill Livingstone, Edinburgh

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Webber BA, **Pryor JA** 1993 Physiotherapy skills: techniques and adjuncts. In: Webber BA, **Pryor JA** (eds) *Physiotherapy for respiratory and cardiac problems* Churchill Livingstone, Edinburgh

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Pryor JA 1992 Mucociliary clearance. In: Ellis E, Alison J (eds) *Key Issues In Cardiopulmonary Physiotherapy* Butterworth Heinemann, Oxford, Ch 6

Pryor JA 1991 The forced expiration technique. In: **Pryor JA** (ed) *Respiratory Care* Churchill Livingstone, Edinburgh

Pryor JA 1991 *The Flutter VRP1 as an adjunct to chest physiotherapy in cystic fibrosis* Dissertation submitted in partial fulfilment of MSc in research methods, King's College, University of London

Webber BA, **Pryor JA** 1991 *The physical treatment of cystic fibrosis* Cystic Fibrosis Trust, England

Pryor JA 1981 *The forced expiration technique* Thesis accepted for a Fellowship of the New Zealand Society of Physiotherapists

3. Invited papers

Pryor JA 2001 What is 'evidence' for cardiorespiratory physiotherapy? (Editorial) *Journal of the Association of Chartered Physiotherapists in Respiratory Care* 34: 8-9

Pryor JA 2000 How can physiotherapy help the respiratory patient? *Respiratory Disease in Practice* 17(3): 20-23

Pryor JA, Webber BA 1992 Physiotherapy for cystic fibrosis - which technique? *Physiotherapy* 78: 105-108

Pryor JA 1981 The forced expiration technique *Netherlands Tijdschrift voor Fysiotherapie* 91 (12): 366-370

4. Abstracts/Letters

Pike SE, Machin AC, Dix KJ, **Pryor JA**, Hodson ME 1999 Comparison of flutter VRP1 and forced expirations (FE) with active cycle of breathing techniques (ACBT) in subjects with cystic fibrosis (CF) *The Netherlands Journal of Medicine* 54: S55-S56

Pryor JA 1997 Current approaches in physiotherapy *Respiratory Medicine* 91: A59-A61

Webber BA, **Pryor JA** 1996 Forced expiration technique (letter) *Pediatric Physical Therapy* 8: 101

Webber BA, **Pryor JA** 1989 Respiratory physiotherapy for cystic fibrosis (letter) *Journal of Pediatrics* 115: 167

Webber BA, **Pryor JA** 1989 Chest Physiotherapy (letter) *British Medical Journal* 298: 827.

Chapter I. Introduction

Cystic fibrosis is the most common, life threatening, inherited disease in the United Kingdom (Cystic Fibrosis Trust 2005). It is an autosomal recessive genetic disorder and in the United Kingdom 2.3 million people are carriers of the faulty cystic fibrosis gene, that is 1 in 25 of the population. There are currently over 7,500 people with cystic fibrosis in the United Kingdom (Cystic Fibrosis Trust 2005).

If both parents are carriers of the gene there is a one in four chance of a child being born with cystic fibrosis (Anderson & Goodchild 1976) (Figure 1.1).

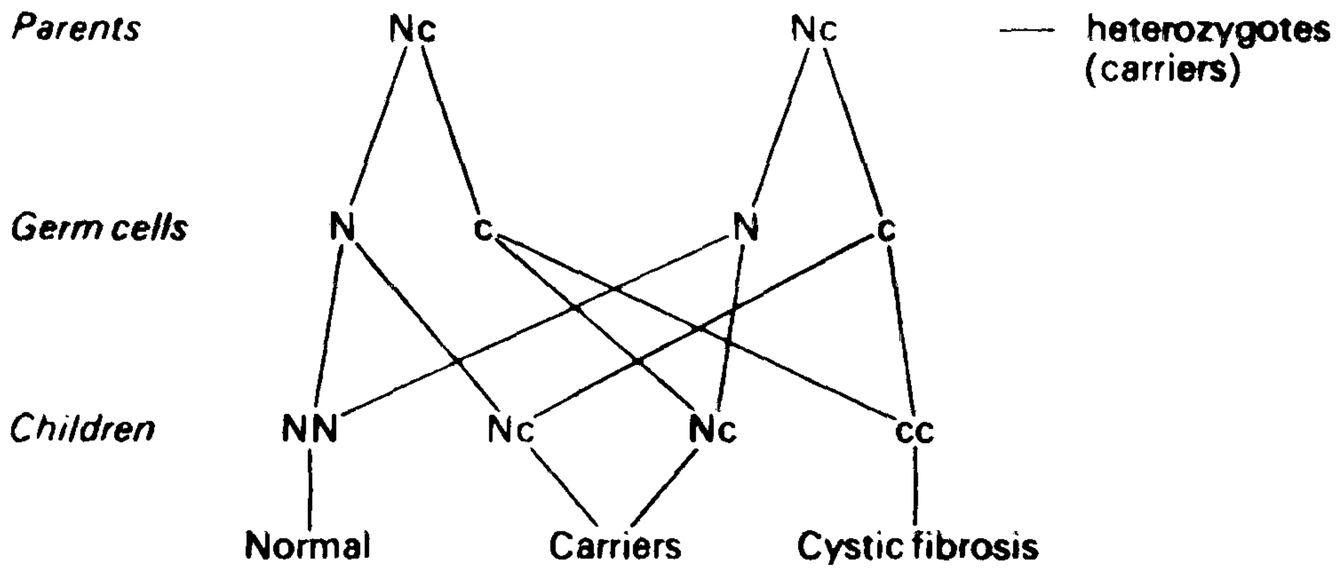


Figure 1.1: Inheritance pattern. N: normal gene, c: cystic fibrosis gene. From: Anderson & Goodchild 1976.

The first clinical descriptions of the disease were said to have been recorded by Fanconi in 1936 and Andersen in 1938 (Anderson & Goodchild 1976). At the time the clinical features focused on abnormal functioning of the pancreas and life expectancy was less than two years. Identification of the cystic fibrosis gene was completed in 1989 (Kerem *et al* 1989; Riordan *et al* 1989; Rommens *et al* 1989). The gene is located on the long

arm of chromosome 7 and encodes for a chloride channel known as the cystic fibrosis transmembrane conductance regulator (CFTR) which is found in epithelial cells. Although cystic fibrosis affects epithelial cell function in many body systems. it is the respiratory system which is associated with high morbidity and mortality (Hodson 2000).

The cystic fibrosis transmembrane conductance regulator proteins function as membrane-bound active chloride channels and have a major part in the control of the salt concentration in epithelial secretions. The sodium concentration in sweat can be measured and until the advent of genetic testing this was the diagnostic tool for cystic fibrosis. The sodium concentration in sweat is over twice the normal amount in people with cystic fibrosis (Wallis 1997), that is > 70 millimoles per litre.

Since the 1960's, with increased recognition of the disease and improved treatment, the median age of survival has risen from 5 years to over 31 years (Cystic Fibrosis Trust 2005; Shale 1997) and has been predicted to be at least 40 years of age for children born in the 1990's (Elborn, Shale, & Britton 1991). From the Cystic Fibrosis Foundation Patient Registry 2002 (Cystic Fibrosis Foundation 2003) the improvement in actual survival, of people on the register, since 1980 is demonstrated in Figure 1.2.

The clinical signs and symptoms of respiratory disease in cystic fibrosis are variable, but at some point the cough becomes prominent and is usually associated with sputum. With progression of the disease. daily sputum increases and becomes purulent. Blood streaking and haemoptysis as a consequence of chronic infection are not uncommon. Exertional dyspnoea is eventually followed by shortness of breath at rest and

dependence on supplemental oxygen. Respiratory failure is the most common cause of death (Gibson, Burns, & Ramsey 2003).

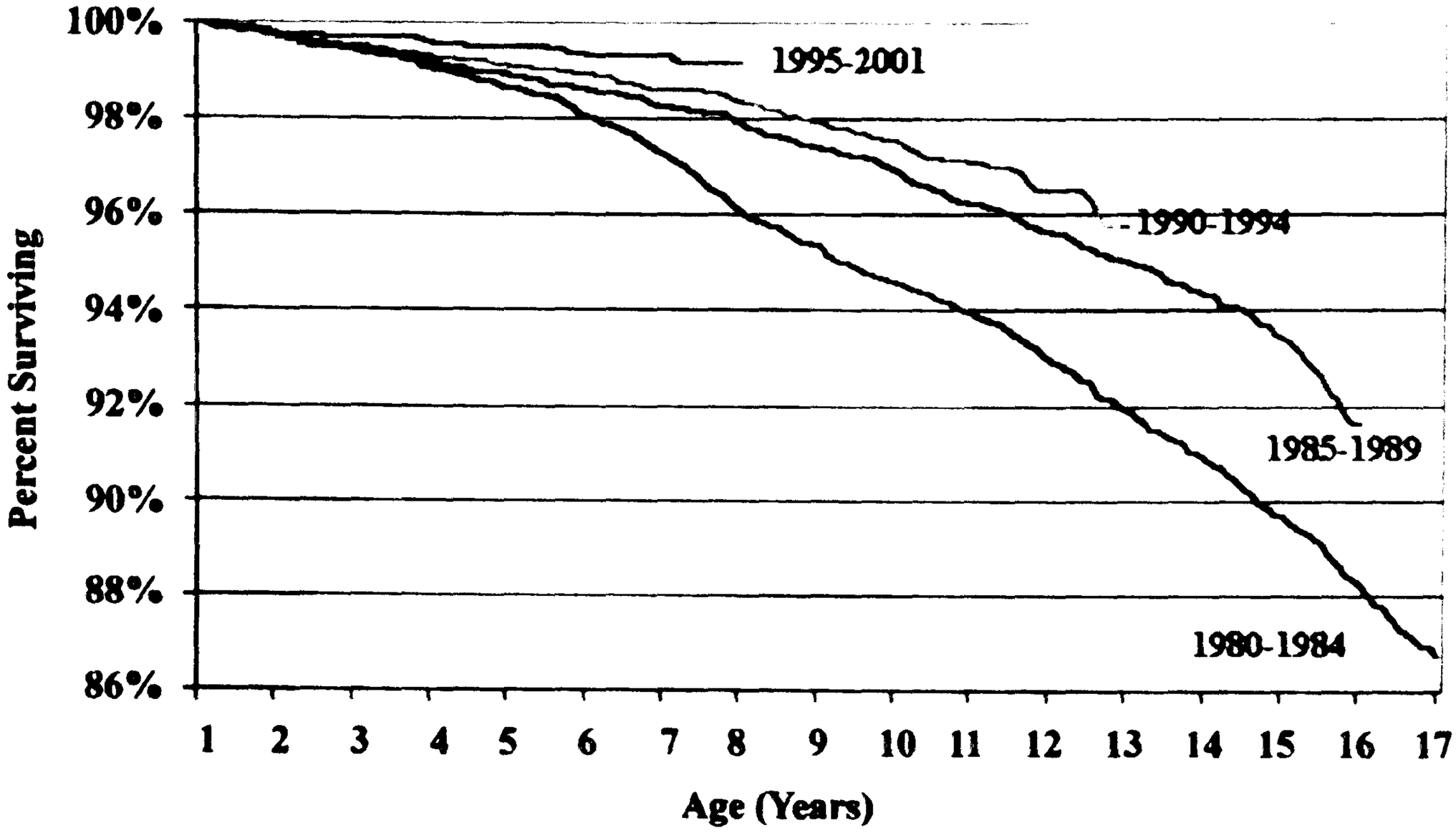


Figure 1.2: Improvement in actual survival. For people born between 1980 and 1984 (blue line) 93 percent were alive at the age of 12 years. For those born between 1990 and 1994 (orange line) 96.5 percent were alive at the age of 12 years. The red line indicates children born between 1995 and 2001 and would indicate a further increase in survival. From: Cystic Fibrosis Foundation 2003.

Early lung infections in people with cystic fibrosis are most frequently a consequence of *Staphylococcus aureus* and *Haemophilus influenzae,* but the most significant pathogen is *Pseudomonas aeruginosa*. *Pseudomonas aeruginosa* demonstrates an increased affinity for cystic fibrosis epithelial cells, although the exact mechanism has yet to be determined (Gibson, Burns, & Ramsey 2003).

With increasing age, people with cystic fibrosis may experience additional complications including those of the older person: diabetes mellitus, osteoporosis, oesophageal reflux and oesophagitis, nasal polyposis, episodic and chronic distal intestinal obstruction syndrome, chronic liver disease, portal hypertension, gallstones, pneumothorax, haemoptysis, allergic bronchopulmonary aspergillosis, respiratory and cardiac failure, inflammatory arthritis, male sub-fertility, and behavioural and psychological problems (Hodson 2000).

Over 1000 candidate mutations in the cystic fibrosis gene have been identified (Cystic Fibrosis Gene Analysis Consortium 2004). There is little apparent correlation between genotype and severity of lung disease. Patients who are homozygous for the delta F508 mutation ('classical' cystic fibrosis) exhibit a wide spectrum in both the rate of deterioration and severity of lung disease (Kerem *et al* 1990; Santis *et al* 1990). This has led to the hypothesis that both environmental-lung interactions and the genetic background of the host contribute to the severity of cystic fibrosis lung disease (modifier genes) (Boucher 2004).

There are two hypotheses regarding the link between epithelial ion transport and the innate defence of the airways against inhaled bacterial pathogens (Boucher 2004):

1. Isotonic volume hypothesis (Mechanical clearance): This is the capacity of the epithelium to maintain the periciliary liquid layer at the appropriate height. This requires adjustment of the airway surface liquid volume which is believed to be mediated by isotonic volume transport.

2. Low salt / defensin hypothesis (Chemical shield): In the human lung an endogenous antibiotic, human β-defensin, may play an important part in preventing pulmonary infection. Human β-defensin is inactivated by increased concentrations of sodium chloride. The high concentrations of sodium chloride in the airway surface liquid of people with cystic fibrosis would allow proliferation of bacteria in the lungs (Goldman *et al* 1997; Rosenstein & Zeitlin 1998). This suggests that bacterial colonisation is the primary event and hypersecretion of mucus occurs as a consequence.

On balance the isotonic volume hypothesis appears to be favoured (Boucher 2004). The steady state of the periciliary liquid is probably dependent on a balance between sodium absorption and chloride secretion. In cystic fibrosis there is evidence of an up regulation of sodium transport and a down regulation of chloride transport, into the airway epithelia. These abnormalities would lead to depletion of the periciliary liquid layer and the formation of thickened mucus plaques and plugs adherent to cystic fibrosis airway surfaces. Depletion of the periciliary liquid reduces the efficiency of ciliary-dependent mucus clearance and a further reduction in ciliary efficiency may be a consequence of the less favourable viscoelastic properties of the concentrated mucus layer for transport (Boucher 2004).

The end result is that of persistent neutrophil dominated airway inflammation with elevated interleukin-8 and neutrophil elastase. This leads to increased mucus production and infection with progressive lung tissue damage. The airways become dilated and bronchiectatic. In the later stages, the lung parenchyma becomes affected by atelectasis, pneumonia and encroachment by enlarging airways. Secondary consequences include hypertrophy of the bronchial circulation and formation of bronchial cysts. Pulmonary

hypertension may ensue (Gibson, Burns, & Ramsey 2003). Cystic fibrosis primarily affects the airways and submucosal glands with sparing of the interstitium and alveolar spaces until late in the disease (Tomashefski *et al* 1989). Earlier work by Tomashefski *et al* (1986) demonstrated that the lung disease and remodelling in cystic fibrosis lungs was irregularly distributed and that the upper lobes were disproportionately affected.

The thick secretions in cystic fibrosis airways result in part from the degradation of the numerous inflammatory cells found in the presence of infection. The deoxyribonucleic acid from these cells tends to aggregate and further increase mucus viscosity. Nebulised recombinant human deoxyribonuclease (Dornase alfa) reduces the viscoelasticity of mucus, by cleaving extracellular neutrophil-derived deoxyribonucleic acid, and has been shown to improve lung function and to reduce exacerbations of infection in people with cystic fibrosis (Hodson *et al* 2003).

Gene therapy holds potential for the future management of people with cystic fibrosis, but a curative treatment has yet to be realised. Current therapy is directed at slowing the progression of secondary organ dysfunction and the consequences of pancreatic insufficiency and chronic endobronchial infection. A normal CFTR gene can be produced, but the problem has been to incorporate the gene into the airway cells and to stimulate its expression into functioning CFTR *in vivo* (Middleton & Alton 1998). Both liposomes and genetically modified adenovirus vectors have been used to transfer the gene, but the functional effect has been poor with only transient or small changes in CFTR expression. Viral vectors are the more effective, for incorporating the new gene into the epithelial cell, but have been associated with significant inflammatory reactions (McElvaney & Crystal 1995). A recent review (Griesenbach, Geddes, & Alton 2004) is

more encouraging stating that considerable progress has been made in pre-clinical research, including the development of new viral and non-viral transfer agents.

As bronchial infection and respiratory failure remain the main cause of morbidity and mortality in people with cystic fibrosis (Gibson, Burns, & Ramsey 2003; Hodson 2000), the physiotherapy management of airway clearance is internationally accepted as a very important component in the medical management of these people. The main function of an airway clearance regimen is to assist the removal of tracheobronchial secretions, the purpose being to reduce airway obstruction and airway resistance, to enhance gas exchange and to reduce the work of breathing (Wallis & Prasad 1999). In the long term, reduction of elastase mediated damage to the airways may slow the rate of progression of lung damage and consequent impairment of mucociliary clearance (Zach 1990).

There is debate as to when airway clearance techniques should be introduced if the infant or young child is asymptomatic (Pryor *et al* 2005). It is likely that the newly born infant has normal lung structure, but repeated episodes of infection and / or aspiration lead to respiratory inflammation and lung injury (Birrer *et al* 1994). There is evidence of pulmonary inflammation and infection from three months of life (Armstrong *et al* 1995) and adults with minimal symptoms of lung disease show respiratory inflammation (Konstan *et al* 1994) even without signs of active infection.

Most adults will have either a chronic productive cough or a history of repeated chest infections and there is international agreement (International Physiotherapy Group for Cystic Fibrosis (IPG/CF) 2002) that best practice is the establishment of an effective airway clearance regimen from the time of diagnosis. Exercise is known to increase mucociliary clearance, although it is not as effective as the airway clearance technique

of the active cycle of breathing techniques (Salh *et al* 1989), but for some people with mild disease the increase in mucociliary clearance, from physical activity, may be sufficient in the absence of signs and symptoms of respiratory infection. Exercise however has additional positive effects on exercise capacity, strength, lung function and quality of life (Bradley & Moran 2004).

A number of meta-analyses and reviews have studied the effects of airway clearance techniques in people with cystic fibrosis (Butler & Sutherland 1998; Eid *et al* 1991; Hardy *et al* 1994; Hess 2001; Langenderfer 1998; McIlwaine & Davidson 1996; Prasad & Main 1998; Williams 1994). They conclude that there is a dearth of high level evidence to support the efficiency and consequences of any airway clearance technique. The selection criteria for the most appropriate regimen for an individual and the problems associated with the treatment related burden an airway clearance regimen imposes remain unclear. This may be due to many of the studies being small, usually short term, many using the cross-over design and few using a control group.

However Thomas, Cook, & Brooks (1995) concluded that postural drainage and percussion resulted in significantly greater sputum expectoration than no treatment and that postural drainage and percussion, when combined with exercise, were associated with a moderate increase in forced expiratory volume in one second, compared with postural drainage and percussion alone. A reduction in forced expiratory volume in one second has been recognised as a predictor of mortality in people with cystic fibrosis (Kerem *et al* 1992). Two earlier studies had shown postural drainage, percussion and vibration to be effective in slowing the deterioration of lung function in people with cystic fibrosis (Desmond *et al* 1983; Reisman *et al* 1988) and the introduction of the active cycle of breathing techniques had been shown to improve lung function (Webber

et al 1986).

A Cochrane review (van der Schans, Prasad, & Main 2004) compared chest physiotherapy (postural drainage and percussion) with no chest physiotherapy. for people with cystic fibrosis. This review concluded that airway clearance techniques have short term effects in terms of increasing mucus transport, but no evidence was found on which to draw conclusions concerning the long term effects.

Another Cochrane review (Elkins, Jones, & van der Schans 2004) looked at positive expiratory pressure for airway clearance in people with cystic fibrosis. This review concluded that there was no clear evidence that positive expiratory pressure was a more or less effective intervention overall than other forms of physiotherapy. There was limited evidence that positive expiratory pressure was preferred by participants, compared with other techniques. However this finding is from studies of low quality and the other techniques included postural drainage and percussion which require an assistant.

A later Cochrane review compared 'conventional' chest physiotherapy (postural drainage and percussion) with other contemporary airway clearance techniques. There appeared to be no advantage of 'conventional' chest physiotherapy over other airway clearance techniques in the primary outcome measure of lung function. There was an indication that individuals prefer self-administered regimens (Main, Prasad, & van der Schans 2005).

The primary meta-analysis used in a Cochrane review is on data from randomised controlled trials, but more recently the generic inverse variance method for meta-

analysis of data from cross-over trials and data from parallel-designed trials have been included for comparison (Main, Prasad, & van der Schans 2005).

In most countries postural drainage and percussion have been replaced by airway clearance regimens which can be used independent of an assistant. This followed studies that have shown the independent regimens to be equally effective as, or more effective than, postural drainage and percussion (Falk *et al* 1984; Konstan, Stern, & Doershuk 1994; McIlwaine *et al* 1997; Pryor *et al* 1979).

There continues to be widespread debate as to which airway clearance regimen should be used and when (Lapin 2000) and in spite of some evidence in support of the efficacy of an airway clearance regimen, compliance is often poor (Abbott *et al* 1994; Muszynski-Kwan, Perlman, & Rivington-Law 1988; Passero, Remor, & Salomon 1981). This may in part be due to the short-comings of postural drainage and percussion, for example lengthy treatment sessions and the need for a skilled provider (Oermann *et al* 2001).

Oermann et al (2001) have developed an instrument to measure patient satisfaction with chest physiotherapy in people with cystic fibrosis. Their results identified differences among the chest physiotherapy regimens of postural drainage, percussion and vibration, high frequency chest wall oscillation and the flutter. For overall satisfaction, the flutter and high frequency chest wall oscillation outscored postural drainage, percussion and vibration. In the convenience domain, the flutter scored higher than high frequency chest wall oscillation. For efficacy, high frequency chest wall oscillation scored the highest and for comfort, the flutter was better tolerated than high frequency chest wall oscillation. The authors concluded that the reasons for these differences were

multifactorial and supported the need to individualise airway clearance regimens.

Increased longevity has been associated with improved quality of life and many people with cystic fibrosis lead normal, busy lives at work and at play. It is important that time spent on treatment is beneficial. Airway clearance can be undertaken independent of an assistant, but considerable time is spent on airway clearance and different airway clearance regimens are used. There is evidence that the active cycle of breathing techniques, autogenic drainage, cornet and positive expiratory pressure are equally as effective in the short term, but are they equally effective in the long term? There is a dearth of long term randomised controlled trials in airway clearance.

Aim of the study

The aim of the study was to evaluate the long term (one year) effects of the airway clearance techniques of the active cycle of breathing techniques, autogenic drainage, cornet, flutter and positive expiratory pressure in people with cystic fibrosis, and to identify any differences which may exist among them.

The primary outcome measure was:

- Forced expiratory volume in one second (FEV_1).

The secondary outcome measures were:

- Forced vital capacity (FVC), maximal expiratory flow at 25% of forced vital capacity (MEF_{25}) and residual volume as a percent of total lung capacity (RV%TLC)
- Body mass index (BMI)
- Exercise capacity (Modified Shuttle Test)
- Quality of life (Short Form-36 and Chronic Respiratory Questionnaire)
- Time for treatment
- Adherence to treatment
- Courses of intravenous antibiotics.

Null hypothesis

The null hypothesis was that there are no significant differences among the airway clearance regimens of the active cycle of breathing techniques, autogenic drainage, cornet, flutter and positive expiratory pressure, over a period of one year.

Chapter II. Airway Clearance Techniques: the literature

Historical perspective

Under normal physiological conditions, the movement of mucus secretions in the airways is efficiently undertaken by the cilia, regular breathing movements and the occasional cough. However changes in the quantity of mucus, in the characteristics of mucus or changes in lung physiology may overwhelm the mucociliary escalator (Lapin 2002).

The use of airway clearance techniques to augment the normal mucociliary and cough clearance mechanism of the lungs is not new. Ewart in 1901 published three cases where he had instigated treatment 'by posture and by respiratory exercises' for people with bronchiectasis. His first case benefited considerably from 'the relative luxury of rest and hospital treatment', but the winter of 1900 brought a return of the patient's signs of a high fever, severe cough and expectoration of sputum. The patient was 'prevailed upon' to lie down and Dr Ewart raised the foot of the bed. It was said that expectoration began to flow easily and the patient was much relieved. Figure 2.1 shows the dramatic effect on the patient's temperature following the raising of the foot of the bed on 26 October 1900.

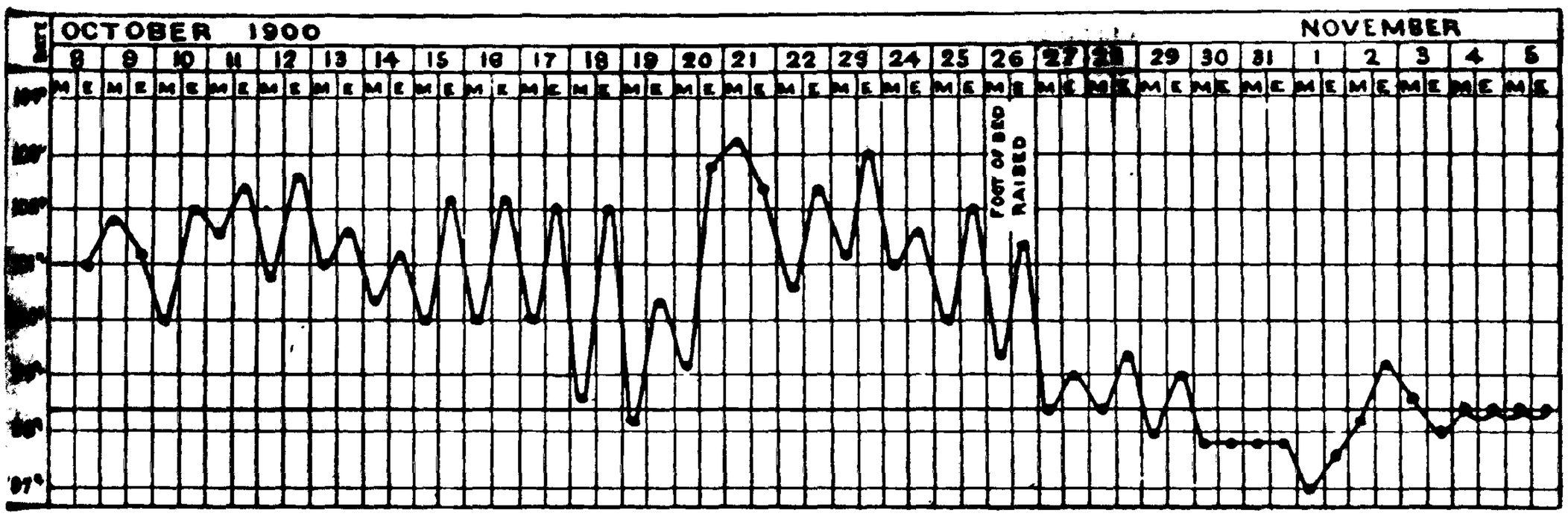


Figure 2.1: The effect of the head-down tipped position on temperature in a patient with bronchiectasis. From: Ewart 1901.

Ewart recommended either continuous drainage or, as in the case of a woman who was seven months pregnant, drainage of an hour two or three times a day. Ewart credits the originality of the technique to Quinke who published a description of this form of treatment in 1898 in 'Zeitschrift für Krankenpflege' (August 1898 p.525).

By 1976 physiotherapy had become an established part of the management of people with cystic fibrosis (Anderson & Goodchild 1976). Anderson and Goodchild state that adequate and consistent physiotherapy may well be the single most important factor in preventing chronic lung infection and in aiding antibiotics to eradicate infection once this has occurred.

The main features of physiotherapy at this time, as documented by Anderson and Goodchild (1976), were:

1. Efforts are made to loosen sputum in all areas of the lung fields.
2. The patient is placed in *five basic positions*, as illustrated (Figure 2.2).

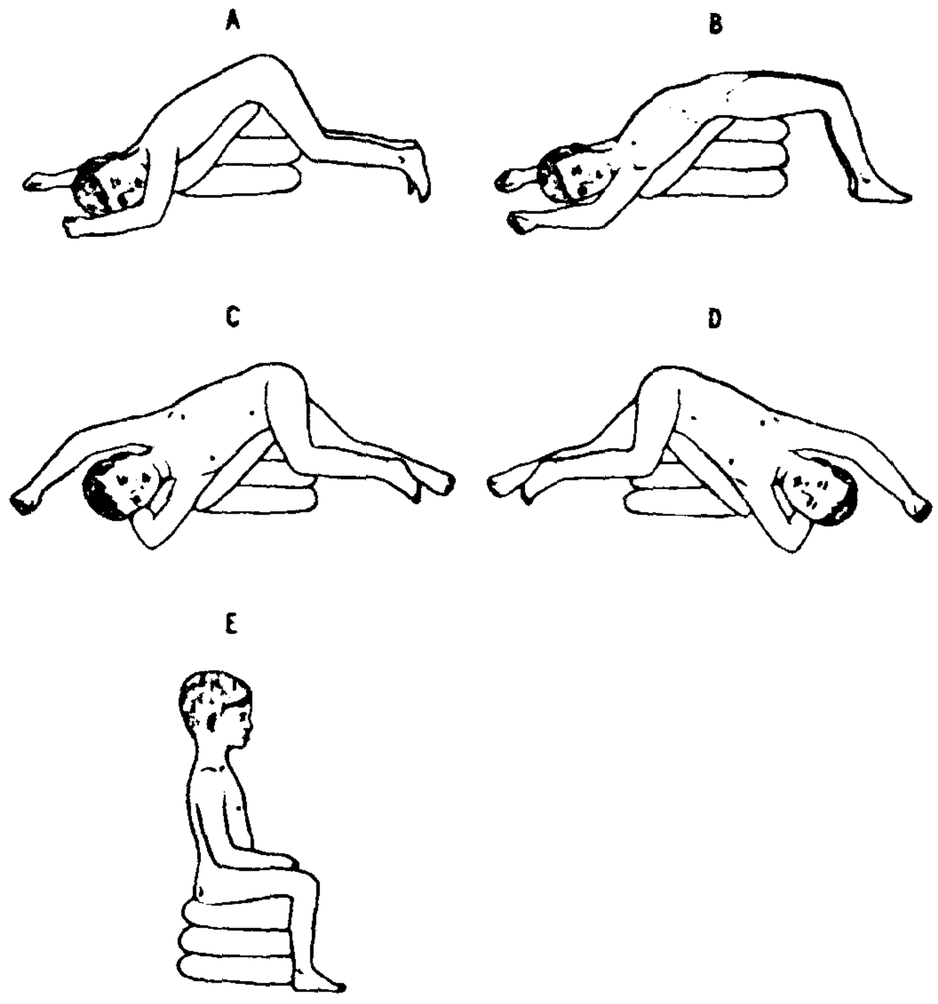


Figure 2.2: The 'five basic' postural positions.

3. *Percussion* of the chest is extremely important, using cupped hands, for 2-3 minutes in *each of the positions* so that the total time is about 15-20 minutes.
4. In older children able to co-operate, a few minutes of *vibrations and rib springing* in each position are beneficial.
5. The patient is encouraged to *expel secretions* by coughing between each change of position.
6. The *most effective time for physiotherapy is the early morning before breakfast* so that secretions accumulated during the night are expelled. Most should have a second treatment in the evening and if the child has a cold or fresh chest infection, or is severely affected and has copious sputum, a third, possibly shorter, treatment at midday or at 4 p.m. on returning from school.
7. This treatment should be given *before meals* to avoid vomiting which may be induced by the changes in position and by swallowed sputum.

   If babies should vomit, care should be taken to give extra feeds so that total caloric intake can be maintained.

8. *Positioning.* Babies and small children can be treated over the knee, while older children can lie over pillows of a bundle of newspapers covered by a pillow.
9. Apart from the above, *simple breathing exercises* and *effective coughing* should be taught as soon as possible. Older children with restricted thoracic movement and poor posture should be taught thoracic mobilizing exercises and correct posture.
10. *Participation in as many physical activities* and games as patients feel able to manage should be encouraged, as these all help to clear secretions from the lungs.
    Swimming is especially helpful.
    Trampolines for young children are very effective in loosening bronchial secretions.

Postural drainage and percussion, as an airway clearance regimen, has remained the 'gold standard' of airway clearance in the United States of America (Accurso *et al* 2004), but other airway clearance regimens have evolved, independently, in different parts of the world – active cycle of breathing techniques (New Zealand and the United Kingdom), autogenic drainage (Belgium), cornet (Germany), flutter (Switzerland) and positive expiratory pressure (Denmark). In addition, high frequency chest wall oscillation is widely used in the United States and Canada, and intra-pulmonary percussive ventilation is used in parts of the United States, Canada and Europe.

The Cystic Fibrosis Trust (United Kingdom) has published 'Clinical Guidelines for the Physiotherapy Management of Cystic Fibrosis' (Association of Chartered Physiotherapists in Cystic Fibrosis 2002). The section on airway clearance techniques includes the active cycle of breathing techniques, autogenic drainage, positive expiratory pressure and oscillating positive expiratory pressure (cornet and flutter).

Forced expiration technique

Livingstone and Gillespie discussed the value of breathing exercises in asthma over 70 years ago (Livingstone & Gillespie 1935). They had recommended 'a *short* inspiration through the nose and then a *long* expiration through the mouth, with a whistling or hissing noise'. This was combined with re-education of diaphragmatic movements and may be one of the first publications on what we now recognise as the 'forced expiration technique'. Following this publication there was little reference to the use of a controlled forced expiratory manoeuvre in airway clearance until the publication of the peer review paper 'Forced expiration exercises in asthma and their effect on FEV_1' by Thompson and Thompson in 1968. At the time there was international criticism of the Thompsons' work in this field.

Mr Heath Thompson was a Cardiothoracic Surgeon, Respiratory Physician and Intensivist at the Christchurch Hospital and The Princess Margaret Hospital in Christchurch, New Zealand. Today these are separate professional specialities. Mrs Bernice Thompson was a New Zealand trained physiotherapist with her own private Thoracic Physiotherapy Practice in Christchurch, the first of its kind in New Zealand. Mr and Mrs Thompson had worked in Sully Hospital, Wales, following Mr Thompson's postgraduate training as a Thoracic Surgeon, in London, and before they both returned to New Zealand to practise. The Medical Superintendent at Sully Hospital (1950 – 1953) was also a New Zealander, Dr Foreman, and the Head of Physiotherapy was Verna Davies. At Sully Hospital, huffing was used to 'raise mucus where there was collapse or danger of collapse of lobes' together with correction of the breathing pattern (Thompson 2004). Chest compression and chest shaking were used if indicated and patients were treated in the sitting position (Thompson 2004). Many of the patients had

tuberculosis and were seen following thoracic surgery (lobectomy and pneumonectomy), but little had been published and the technique of 'huffing' was later disregarded in the United Kingdom.

A significant proportion of Mrs Thompson's patients in her practice in New Zealand had asthma. It is important to remember that the pharmacological management of asthma was not as effective as it is today and most patients with asthma, in the 1960's and early 1970's, presented with cough and a moderate amount of sputum in addition to wheeze. It was the use of forced expiration exercises as an airway clearance technique in asthma that the Thompsons reported in 1968 and this was very controversial at the time.

The paper by Thompson and Thompson (1968) begins:

> 'Many authorities say that forced or prolonged expiration in the treatment of asthma is wrong..... Forced expiration by producing an accentuation of the normal expiratory movements of the bronchial tree, i.e. narrowing and shortening, squeezes mucus from the small peripheral to the larger central bronchi..... We believe that mucus is moved in the more peripheral bronchi, not by a blast of expired air, but by the squeezing action of the narrowing and shortening of the bronchial tree during forced expiration – the peripheral branches shortening towards the central bronchi'.

These statements were supported by cine-radiography (Figure 3.3, p.92). The technique advocated was that of a 'mix' of forced expiration and breathing control (diaphragmatic breathing) often combined with postural drainage. Attention was also paid to postural and mobilising exercises, and to nose blowing. It was said that the forced expiration should be performed as 'vigorously as possible'. The techniques are delightfully outlined in Bernice Thompson's books 'Asthma and your child' and 'Better Breathing'

(Thompson 1963; Thompson 1967). An example of one of the little cartoon characters which illustrate the text is reproduced in Figure 2.3.

CHUFFY THE ENGINE

Once upon a time there was a little engine and his name was Chuffy. Sometimes he made a big noise that went Chshshshsh! Put your hands on your shoulders. Now lean forward and punch while you make your noise.

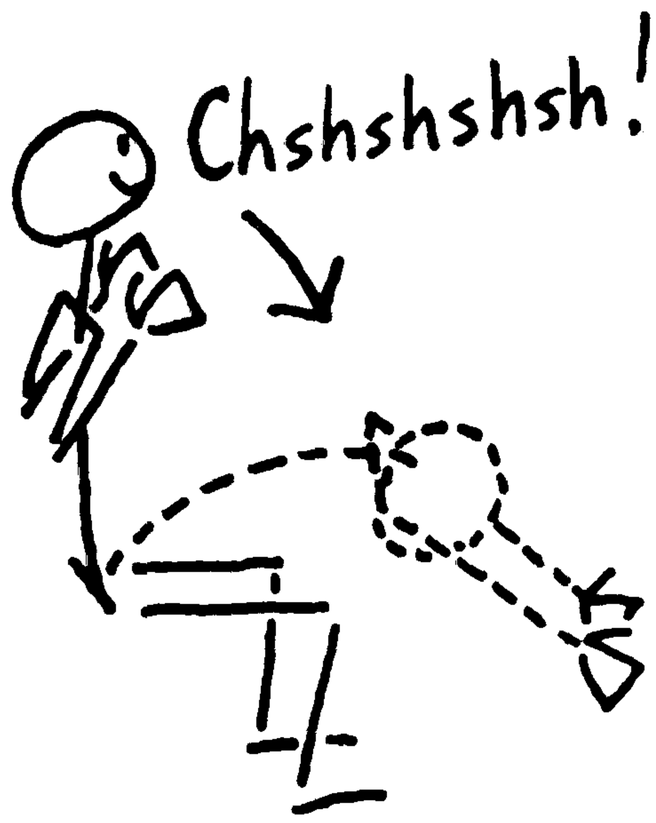


Figure 2.3: Breathing exercise for asthma. From: Thompson 1963.

In the study by Thompson & Thompson (1968) patients were tested over a two-month period. The pulmonary function measure of forced expiratory volume in one second (FEV_1) was taken before and after treatment with breathing exercises, for 111 subjects. The time interval of the measurement following treatment is not recorded, but bronchodilator therapy was withheld before treatment on that day. Ninety-one of the 111 patients demonstrated an improvement in FEV_1 on their initial test. Only four remained unchanged on later testing. The details available are outlined in Table 2.1.

Thompson & Thompson 1968 N = 111 (Age range: 2-20 years)	
Initial testing	**Later testing**
91 demonstrated improvement in FEV_1	-
6 demonstrated no change in FEV_1	2 improved, 4 no change in FEV_1
14 demonstrated a reduction in FEV_1	14 demonstrated improvement in FEV_1
% improvement in FEV_1: 0 – 150% (Mean: 33%)	

Table 2.1: Data from 'Forced expiration exercises in asthma and their effect on FEV_1' (Thompson & Thompson 1968).

It was concluded that following treatment using forced expiration and breathing control, the airways were less obstructed. The improvements demonstrated on later testing were thought to be a consequence of more efficient airway clearance with regular daily practice of the exercises.

In 1972 Mrs Thompson presented her work at the World Congress of Rehabilitation, in Sydney, Australia. This paper (Thompson 1973) received international criticism. It was claimed that the exercises would increase airflow obstruction and should not be used. The paper was descriptive, but 'stills' taken from a piece of x-ray movie film (Figure 3.3, p.92), during a bronchogram, demonstrate the squeezing of the radio-opaque material from the distal branches to the main bronchi, with a forced expiration. The narrowing of the lobar bronchi and ineffective movement of distal secretions by a cough were also demonstrated.

Mrs Thompson stated that the exercises themselves were not new, but their application to the treatment of asthma was new. She emphasised that the length and strength of the expiration needed to be gauged to each person's ability to produce a feeling of contraction without provoking a cough. It was 'mixed' carefully with diaphragmatic breathing. Mrs Thompson had identified that coughing released mucus largely from the upper airways and that the more 'dynamic' form of postural drainage using forced expiration took 'only a few minutes as opposed to 20 to 30 minutes of passive postural drainage'. The technique was practised in Christchurch, New Zealand, but was not widely taken up elsewhere.

Jennifer Pryor was privileged to be one of the physiotherapy students and physiotherapy graduates to be trained by the Thompsons. The technique was clinically effective in all patients with excess bronchial secretions and in the Christchurch Hospitals, in the 1970's, the Thompson technique was the recognised airway clearance technique, the 'gold' standard. At the Brompton Hospital, in the 1970's, huffing was used on the surgical wards, but was not accepted practice on the medical wards as it was said to increase airflow obstruction in patients with medical chest problems.

During the 1970's the life expectancy of people with cystic fibrosis was increasing. It was becoming a disease of the adolescent and young adult. The airway clearance regimen was assisted postural drainage. The description, in 'The Brompton Hospital Guide to Chest Physiotherapy' (Gaskell & Webber 1973) was:

> 'The patient is positioned to assist the drainage of secretions from specific areas of the lungs by means of gravity. The positions are based on the anatomy of the bronchial tree... This drainage should be assisted by vibratory shaking or percussion of the chest, combined with localised breathing exercises... The appropriate positions should be maintained for up to half an hour 2-6 times a day, according to the individual patient's needs'.

If children with cystic fibrosis wished to spend a night away from home and their parents, someone had to be taught chest clapping. This was usually possible when the child was staying with friends or relatives, but was becoming increasingly difficult when the adolescent was considering college or university. Mr Kenneth Flower, an engineer at Salford University (England), was aware of this problem and designed a postural drainage frame with a mechanical percussor (a modified Black and Dekker® drill) as an alternative regimen (Figure 2.4).

a.



b.



Figure 2.4: Postural drainage frame and mechanical percussor. a. Frame in use. The white arrow denotes the position of the mechanical percussor. b. Returning to the upright position to cough.

Mr Flower approached the Brompton Hospital, which had established the first Adult Cystic Fibrosis Unit in the United Kingdom, to ask if this regimen could be assessed.

The challenge was accepted and a cross-over study designed. There were three arms to the study:

1. Conventional postural drainage: Postural drainage using thoracic expansion exercises combined with chest clapping and shaking by a physiotherapist. The subject was encouraged to cough when secretions reached the upper airways (Treatment A) (Gaskell & Webber 1973).

2. Postural drainage using huffing combined with breathing control (the forced expiration technique) with thoracic expansion exercises, coughing, and chest clapping and compression by the subject himself (Treatment B).

3. Postural drainage using a full length frame and mechanical percussor (Figure 2.4). The subject coughed when secretions reached the upper airways.

The number of monitored treatment sessions ranged from two to four. The third regimen, that of the postural drainage frame and mechanical percussor, had to be discontinued. In the 1970's the nutritional management of people with cystic fibrosis was different from that of today and many were thin and undernourished. The mechanical percussor was not well tolerated by the patients, and the frame and percussor were cumbersome and noisy.

More sputum was expectorated in a shorter period of time using Treatment B which included huffing and breathing control (Table 2.2 and Figure 2.5).

Results:

Pryor *et al* 1979 N = 18 (mean age: 20.5 years)			
	Treatment A Mean (SEM)	**Treatment B** Mean (SEM)	p-value
Total time for treatment in one day (minutes)	127.0 (8.25)	99.4 (5.76)	$p<0.01$
Weight of sputum expectorated during treatment sessions in one day (grams)	45.6 (5.76)	63.1 (6.92)	$p<0.025$
Rate of sputum clearance (milligrams / minute)	358.5 (36.13)	652.1 (64.1)	$p<0.005$

Table 2.2: Results Part I (Pryor *et al* 1979). Treatment A: Conventional postural drainage with an assistant. Treatment B: Postural drainage using the forced expiration technique without an assistant.

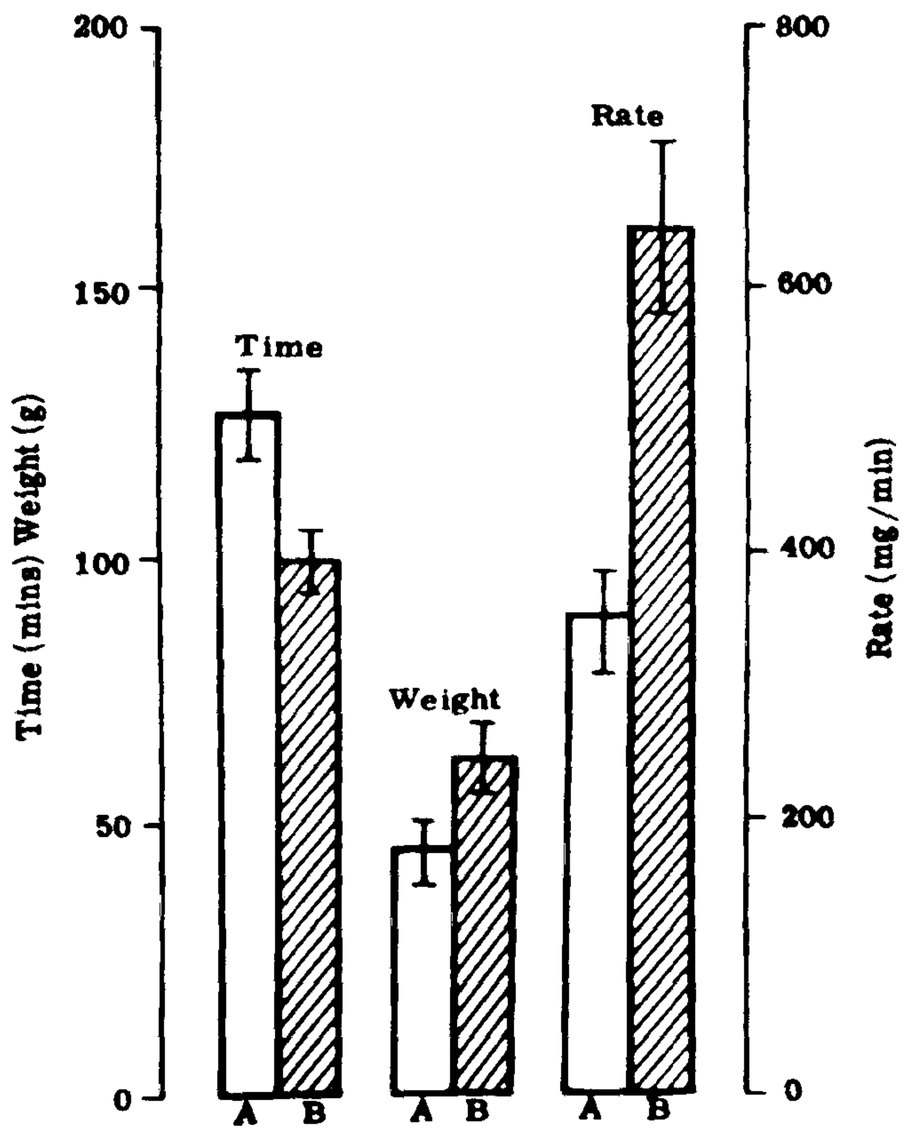


Figure 2.5: Mean ± SEM time for treatment, weight of sputum expectorated during treatment and rate of sputum clearance during treatment sessions in one day. Treatment A: Conventional postural drainage with an assistant. Treatment B: Postural drainage using the forced expiration technique without an assistant (Pryor *et al* 1979).

As a consequence of discontinuing the regimen with the mechanical percussor and postural drainage frame, there were two variables in the study:

1. An assistant (Treatment A) and no assistant (Treatment B)
2. The use of the forced expiration technique (Treatment B) and the absence of the forced expiration technique (Treatment A).

It was important to identify the role of the assistant. Treatment B was compared with Treatment C (Postural drainage using the forced expiration technique with an assistant) (Table 2.3).

Results:

Pryor *et al* 1979 N = 8 (mean age: 23.9 years)			
	Treatment B Mean (SEM)	**Treatment C** Mean (SEM)	p-value
Time for treatment in one day (minutes)	98.3 (5.63)	95.3 (5.61)	NS
Weight of sputum expectorated during treatment sessions in one day (grams)	46.4 (6.2)	44.6 (4.61)	NS
Rate of sputum clearance (milligrams / minute)	493.1 (69.04)	482.2 (52.13)	NS

Table 2.3: Results Part II (Pryor *et al* 1979). Treatment B: Postural drainage using the forced expiration technique without an assistant. Treatment C: Postural drainage using the forced expiration technique with an assistant.

It was concluded that when clinically stable, people with cystic fibrosis could do their own postural drainage effectively without an assistant (Pryor *et al* 1979). The results of this study changed clinical practice. Adolescents with cystic fibrosis could be trained to do their own physiotherapy independently. This had a big impact on quality of life

opening up opportunities for holidays independent of parents, college and university. These studies did not however indicate that people could be equally as effective on their own during an acute pulmonary exacerbation of infection.

The above studies had demonstrated that the inclusion of the forced expiration technique together with postural drainage (the use of gravity assisted positioning) increased the effectiveness and efficiency of airway clearance in people with cystic fibrosis. The lung function values of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF) were recorded before and 30 minutes following treatments A, B and C. There were no significant differences when before treatment lung function values were compared with after treatment values (Pryor *et al* 1979). This indicated that there was no increase in airflow obstruction when huffing and breathing control were included in the regimens. The subjects in these studies were people with cystic fibrosis. In the 1970's these people had copious bronchial secretions and minimal bronchospasm. Would these findings be reflected in people with asthma?

Twenty patients admitted to hospital with asthma were recruited to this study, at the time their cough became productive of sputum.

Treatment D was postural drainage using thoracic expansion exercises and coughing, combined with chest percussion and shaking by a physiotherapist and interspersed with periods of relaxed, diaphragmatic breathing.

Treatment E was postural drainage using the forced expiration technique, thoracic expansion exercises and coughing, combined with chest percussion and shaking by a physiotherapist and interspersed with periods of relaxed, diaphragmatic breathing.

The end point of treatment was when coughing no longer resulted in the expectoration of sputum.

Results:

Pryor & Webber 1979			
N = 20 (mean age: 34.2 years)			
	Treatment D Mean	**Treatment E** Mean	p-value
Time for a treatment session (minutes)	10.5	8.9	$p<0.001$
Weight of sputum expectorated during a treatment session (grams)	3.9	3.7	NS
Rate of sputum clearance (milligrams / minute)	375.0	425.0	NS

Table 2.4: Results Part III (Pryor & Webber 1979). Treatment D: Conventional postural drainage with an assistant. Treatment E: Postural drainage using the forced expiration technique with an assistant.

Lung function (FEV_1, FVC and PEF) was measured before and 30 minutes after treatment. When the lung function data were combined there was a significant improvement after treatment with both regimens ($p<0.001$), but there was a significantly shorter time for treatment when the forced expiration technique was included. These studies were published in the *British Medical Journal* (Pryor *et al* 1979) and in *Physiotherapy* (Pryor & Webber 1979). Clinical practice changed in the United Kingdom, Australia and New Zealand as the use of huffing and breathing control became an accepted component of airway clearance in both medical and surgical chest patients.

Van der Schans *et al* (1994), using an experimental model, confirmed the hypothesis that airway narrowing, as during a forced expiratory manoeuvre, can be used to assist clearance of mucus. As a consequence of this work van der Schans (1997) recommended that forced expiratory manoeuvres should be considered the first treatment for mucus retention as the dynamic compression that occurs during a forced expiration is essential for effective transport of mucus. In conclusion van der Schans implied that this 'mechanistic' approach validated the use of the forced expiration technique and active cycle of breathing technique (sic) in airway clearance.

Active cycle of breathing techniques

The use of the forced expiration technique in airway clearance had always been a component of a cycle of breathing techniques. Bernice Thompson had used it together with positioning, chest clapping, posture and chest wall mobility exercises. Research groups (Falk *et al* 1984; McDonnell, McNicholas, & FitzGerald 1986; Reisman *et al* 1988) misinterpreted the literature (Pryor *et al* 1979; Pryor & Webber 1979) and used huffing in isolation and often without breathing control. It became important to emphasise that huffing must be combined with breathing control, the forced expiration technique, and for many people with excess bronchial secretions it should be used in conjunction with other airway clearance techniques, for example thoracic expansion exercises and positioning if indicated. In an attempt to describe, more accurately, the regimen of the studies of 1979 (Pryor *et al* 1979; Pryor & Webber 1979) a paper was written describing the regimen as the active cycle of breathing techniques (Webber 1990).

It was described as consisting of three breathing techniques:

1. Breathing control
2. Thoracic expansion exercises
3. Forced expiration technique: one or two huffs followed by breathing control.

This, in practice, is exactly the same as the description published in the British Medical Journal (Pryor *et al* 1979):

1. Forced expiration technique: one or two huffs (forced expirations) from mid-lung volume to low lung volume followed by
2. A period of relaxed, controlled diaphragmatic breathing
3. Expansion breathing exercises.

Five years later (Wilson, Baldwin, & Walshaw 1995). in the United Kingdom. undertook a study to compare 'traditional' chest physiotherapy with the active cycle of breathing (sic) in patients with chronic suppurative lung disease as they claimed that no direct comparison between postural drainage with percussion, vibration and breathing exercises and postural drainage combined with the active cycle of breathing techniques had previously been undertaken. This was a cross-over study with 17 subjects (15 had cystic fibrosis, 1 bronchiectasis and 1 Job`s syndrome). The mean age was 24.0 years. The active cycle of breathing (sic) produced significantly more sputum (p=0.013) and took significantly less time to perform (p=0.01). They concluded that the active cycle of breathing techniques was more effective than traditional methods of physiotherapy in clearing sputum from the chest. This was further evidence in support of the study undertaken 16 years earlier (Pryor *et al* 1979) and also in the United Kingdom.

In retrospect it is appreciated that a name change causes considerable confusion in the literature with the use of the electronic searches of today. To access all papers on the active cycle of breathing techniques it is necessary to use the key words of 'forced expiration technique', 'forced expiratory technique', 'active cycle of breathing techniques', ' active cycle of breathing' and 'active cycle of breathing technique'. However in the clinical context the name change allowed the active cycle of breathing techniques to enter Europe. 'It was a good thing you changed the name, we might be allowed to use it now' (Oberwaldner 1991). Prior to this many of the Europeans had remained concerned that the use of forced expirations, in airway clearance, would increase airflow obstruction.

The active cycle of breathing techniques is a cycle of the techniques of (Figure 2.6):

- Breathing control - tidal breathing at the patient's own rate and depth, encouraging use of the lower chest with relaxation of the upper chest and shoulders.

- Thoracic expansion exercises – deep breathing exercises emphasising inspiration, with or without a breath hold at the end of inspiration. Expiration is quiet and relaxed.

- Forced expiration technique – one or two huffs (forced expirations) combined with periods of breathing control. Huffing to low lung volumes will assist in mobilising and clearing the more peripherally situated secretions and when secretions have reached the larger proximal upper airways, a huff or cough from a high lung volume can be used to clear them.

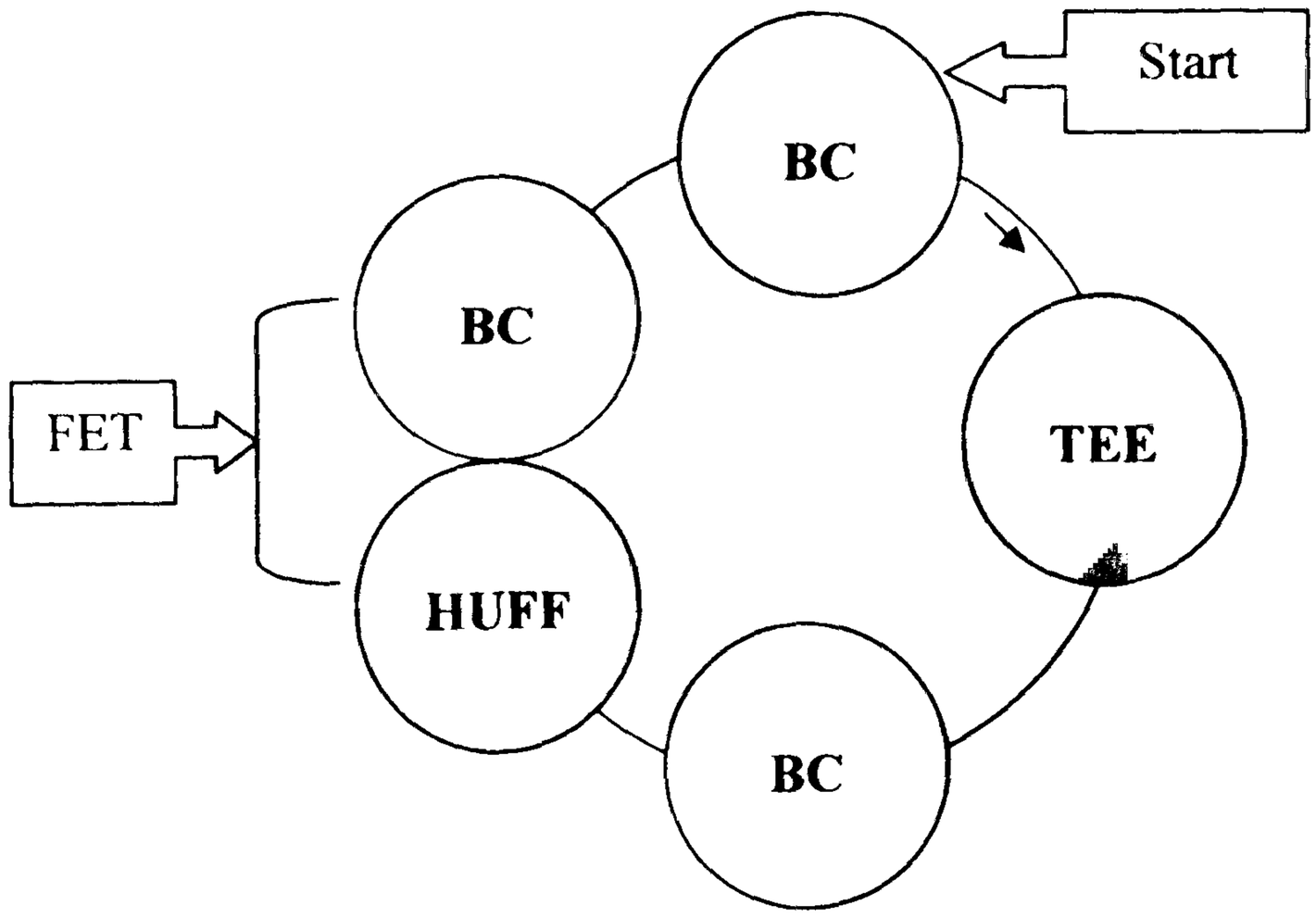


Figure 2.6: The components of the active cycle of breathing techniques: BC - Breathing control, TEE - Thoracic expansion exercises, FET - Forced expiration technique.

The mechanical percussor and postural drainage frame (Figure 2.4, p.40) were not pursued further, but other percussive devices were being developed for use in airway

clearance. The hand-held mechanical percussor (Flower *et al* 1979) was compared with manual self chest clapping in regimens using the forced expiration technique. Twelve patients (mean age: 18.7 years), with cystic fibrosis and undertaking their own treatment, entered this study. There were no significant differences between the two regimens (Pryor, Parker, & Webber 1981).

The next question was whether the component of self chest clapping contributed to the expectoration of sputum and this was studied by Webber *et al* (1985). Postural drainage including thoracic expansion exercises was combined with self chest clapping and interspersed with the forced expiration technique. In 16 patients (mean age: 21.1 years) with cystic fibrosis, this regimen was compared with postural drainage including thoracic expansion exercises interspersed with the forced expiration technique, but without self chest clapping. The authors concluded that there was no greater weight of sputum expectorated during treatment with self chest clapping than treatment without self chest clapping. These patients were clinically stable and the results must not be extrapolated to the patient with cystic fibrosis with an acute pulmonary exacerbation of infection. In these patients, chest clapping by an assistant may be of value.

It was appreciated that the increase in sputum expectorated using the forced expiration technique could have been a consequence of an increase in the salivary component of the expectorated material, or irritation of the bronchial walls causing inflammation and an increase in the amount of mucus secreted by the goblet cells. Sutton *et al* (1983) evaluated the regimens of the forced expiration technique in sitting, the forced expiration technique in the head-down tipped position and directed coughing in sitting in 10 patients with copious sputum production (mean of 63.6 millilitres in 24 hours). The control was the subject resting in the upright (sitting) position. Sputum was

obtained during the 30-minute treatment session and for 30 minutes following treatment. In addition to the measurement of the wet weight of sputum, each sample was freeze dried and the dry macromolecular weight calculated. In all four regimens the ratio of the wet weight of sputum to the dry weight was similar, indicating that the wet weight of sputum reflected tracheobronchial secretions. This result has also been confirmed by Cecins (2000).

Each subject (Sutton *et al* 1983) also inhaled a radioaerosol preparation before the treatment session and this was monitored using an imaging procedure before treatment and 30 minutes following the 30-minute treatment session. All the physiotherapy regimens eliminated more particles from the whole lung than the control, but only following the forced expiration technique in both sitting and in postural drainage positions was this of significance ($p<0.01$). They concluded that postural drainage plus the forced expiration technique was the most effective in airway clearance. Later findings by Verboon, Bakker and Sterk (1986) were contrary to this. They studied the forced expiration technique, in eight adults, but following a night of sleep in the head-down position. They concluded that postural drainage, the following day, conferred no added advantage to an airway clearance regimen of the forced expiration technique under these circumstances.

In 1998, at the University Hospital Nijmegen, The Netherlands, conventional physiotherapy was compared with postural drainage using the forced expiration technique (van Hengstum *et al* 1988). This group concluded that there was no difference in tracheobronchial clearance, regional lung clearance, sputum production or lung function between the two groups.

In 1984 Falk *et al* compared the use of the positive expiratory pressure mask in postural drainage positions and the use of the positive expiratory pressure mask in sitting with two other regimens – the 'forced expiration technique' in postural drainage positions and pursed lipped breathing in the sitting position. Treatment sessions ranged from 20 to 35 minutes and in the regimens where gravity assisted positioning was used, seven positions were undertaken with four to five minutes spent in each position.

The 'forced expiration technique' was '...forced expirations with the glottis open from midway between functional residual capacity and total lung capacity to midway between functional residual capacity and residual volume' which is not 'the' forced expiration technique. It was forced expirations without breathing control and without the flexibility to alter lung volume to loosen and mobilise secretions appropriately. It is not surprising that oxygen tension deteriorated in the regimen of postural drainage and the forced expiration technique (sic) and that the positive expiratory pressure regimen, in sitting, was the one preferred by the patients. Details of this study are reported in the 'Positive expiratory pressure' section of this Chapter (p.79).

Two years later (Hofmeyr, Webber, & Hodson 1986) published the results of a study in which they had compared postural drainage using the forced expiration technique in gravity assisted positions (Treatment A) with positive expiratory pressure in gravity assisted positions (Treatment B) and positive expiratory pressure in sitting (Treatment C), in 18 adults with cystic fibrosis (mean age: 22.5 years). Usually two areas of the lungs were treated in one treatment session. This differs from the seven areas undertaken by Falk *et al* (1984). More sputum was expectorated with the regimen of postural drainage using the forced expiration technique. This group continued with postural drainage using the forced expiration technique in gravity assisted positions.

Details of this study are reported in the 'Positive expiratory pressure' section of this Chapter (p.81).

Reisman *et al*, in Canada in 1988, undertook a 3-year prospective study in 67 children with cystic fibrosis (mean age: 12.2 years). The children were randomised to receive either 'conventional' physiotherapy which comprised postural drainage with percussion and the 'forced expiratory technique' (sic) or physiotherapy using the 'forced expiratory technique' (sic) alone. The forced expiratory technique was 'two maximal inspirations, each followed by a prolonged, controlled, forced expiration, and then three normal quiet inspirations, each followed by a prolonged, controlled, forced expiration'. In the study by Reisman *et al*, it was not surprising that the children using the forced expiratory technique only had a mean annual rate of decline in lung function which was significantly greater than the rate of decline in the 'conventional' physiotherapy group ($p<0.04$).

The intention had been to use the forced expiration technique (Reisman 1989), but there had been no discussion with the proponents of the forced expiration technique and the interpretation of the researchers, from the literature, was incorrect. It had also never been recommended that the forced expiration technique be used in isolation. The papers quoted by Reisman *et al* (Sutton *et al* 1983; Verboon, Bakker, & Sterk 1986) were not the original studies on the forced expiration technique.

Understandably the 'gold' standard in Canada and the United States of America remained postural drainage and percussion (either manual or mechanical). In the United Kingdom there was considerable correspondence and communication regarding the paper by Reisman *et al* (1988). It was said (Freitag 1988) that the paper was 'in print'.

that is it had been peer reviewed and was 'pretty conclusive' as it was a long term study. The differences between the regimens of the 'forced *expiratory* technique' and the 'forced *expiration* technique' were unable to be highlighted until the publication of a letter to *The Journal of Pediatrics* (Webber & Pryor 1989).

Appreciating difficulties in interpretation of the forced expiration technique the characteristics were outlined. A group of nine experienced respiratory physiotherapy clinicians and a senior researcher met to attempt to establish a set of unambiguous descriptors of the technique. The listed items were sent to hospitals in 57 health districts in the United Kingdom and Australia, and physiotherapists in respiratory care were asked to assess the accuracy of the descriptors. The response rate was 63%. The characteristics of effective and ineffective huffing, and effective and ineffective breathing control were summarised (Partridge, Pryor, & Webber 1989) as:

Effective Huffing

1. Mouth open, O-shaped, to keep the back of the throat (glottis) open.
2. (a) A forced expiration from mid-lung volume to low-lung volume (to move the more peripheral secretions).

   (b) A forced expiration from high-lung volume to mid-lung volume (to move the more proximal secretions).
3. Muscles of the chest wall and abdomen contract.
4. Sound is like a sigh, but forced.
5. Rate of expiratory flow varies with the degree of airflow obstruction and disease and is specific to the individual.
6. Crackles will be heard if excess secretions are present.

Ineffective Huffing

1. Mouth half closed or almost closed.
2. Expiration always starting from high-lung volume.
3. Abdominal muscles not used.

4. Sound more like hissing – mouth shape as for 'E' sound, or blowing.
5. Expiration too vigorous or too long, producing paroxysmal coughing. or too gentle, or too short.
6. 'Catching' or 'grunting' at the back of the throat.

Effective Breathing Control

1. Gentle breathing using the lower chest, at normal tidal volume and at a natural rate.
2. Unforced expiration.

Ineffective Breathing Control

1. Use of the upper chest breathing pattern, i.e. accessory muscles.
2. Forced expiration.
3. Breathing above or below tidal volume.
4. Unnatural rate imposed by a physiotherapist.

The amount of sputum expectorated is not the only important outcome measure for an airway clearance regimen. Webber *et al* (1986) studied 12 patients with cystic fibrosis (mean age: 19.25 years) who had been admitted to hospital, but had not previously used the forced expiration technique. Full lung function tests were performed before and three days following the introduction of the airway clearance technique using the forced expiration technique. This was the only change in the patients' management. There were improvements in forced expiratory volume in one second (FEV_1) ($p<0.001$), forced vital capacity (FVC) ($p<0.001$), peak expiratory flow (PEF) ($p<0.001$), peak inspiratory flow (PIF) ($p<0.001$) and maximal expiratory flow at 50% of forced vital capacity (MEF_{50}) ($p<0.025$). It was not ethical to continue this study for more than three days, as the patients either required antibiotics or were ready to be discharged from hospital.

At a later date (Phillips *et al* 1996) the active cycle of breathing techniques was introduced as the only change in the treatment of 58 children with cystic fibrosis, in the

Ukraine. A medical team from the United Kingdom had been invited to assist in the management of these children. Seven months later the children were reassessed by the same medical team. There were significant improvements in oxygen saturation ($p=0.02$) and for those who had previously used a form of airway clearance, the active cycle of breathing techniques was preferred because there was 'less pain', 'increased exercise tolerance' and 'greater independence'.

McDonnell, McNicholas and FitzGerald (1986) demonstrated a fall in oxygen saturation during chest physiotherapy in nine patients with cystic fibrosis (mean age: 19 years) supposedly using the forced expiration technique. The paper does not describe the physiotherapy used, but personal communication with the physiotherapist involved (Concannon 1986) identified a regimen different from postural drainage using the forced expiration technique. Long periods (one minute) of chest clapping were used without thoracic expansion exercises and huffing was not combined with periods of breathing control.

In response to publication of the paper by McDonnell, McNicholas and FitzGerald (1986), the effect on oxygen saturation of postural drainage with the forced expiration technique was studied in 20 patients with cystic fibrosis (mean age: 26.2 years). All subjects were receiving antibiotics for an exacerbation of their bronchopulmonary infection (Pryor, Webber, & Hodson 1990). There were no significant differences in oxygen saturation when values during and after physiotherapy were compared with values before treatment. There was a marginal increase in oxygen saturation during treatment and, contrary to the work by McDonnell *et al*, the oxygen saturation tended to rise during the chest clapping phase which was combined with three or four thoracic

expansion exercises. This represents a much shorter period of time for chest clapping than that used by McDonnell *et al*.

Other devices for airway clearance, in addition to the positive expiratory pressure (PEP) mask, were being developed. The Flutter VRP1 was designed and manufactured in Switzerland and it was requested that this be compared with the forced expiration technique (active cycle of breathing techniques). Twenty-four adults with cystic fibrosis (mean age: 24.4 years) entered this study and twenty completed it. It was a cross-over design comparing the active cycle of breathing techniques alone with a regimen of the active cycle of breathing techniques together with the flutter. The length of time for each monitored treatment session was determined on assessment before entry to the study. The concern was one of sputum retention when the flutter was included in the regimen as there was little spontaneous coughing and little sputum was expectorated during this part of the regimen. The authors (Pryor *et al* 1994) concluded that no advantage was demonstrated by the inclusion of the flutter to a regimen of the active cycle of breathing techniques as measured by sputum clearance, lung function or oxygenation.

In this study (Pryor *et al* 1994) the flutter was used as advocated by the Swiss proponents. The technique was to breathe out through the flutter, but without any forced expiratory manoeuvre. During the study period, the forced expiratory manoeuvre was gaining increasing acceptance in airway clearance in Europe and it was hypothesised by the Swiss that the reduction in sputum expectoration during the use of the flutter may have been a consequence of the absence of huffing. A few years later it was possible to repeat this study combining forced expirations with the flutter technique (Pike *et al* 1999). It was concluded that the flutter and forced expirations, when compared with the

active cycle of breathing techniques, are comparable. The outcome measures were wet weight of sputum, spirometry and oxygen saturation.

High frequency chest compression is widely used as an airway clearance technique in the United States of America (Warwick & Hansen 1991). The Hayek oscillator cuirass has been compared with the active cycle of breathing techniques in ten children with cystic fibrosis (median age: 14 years) admitted to hospital with an exacerbation of infection (Phillips *et al* 2004). There were significantly greater improvements in lung function and in the amount of sputum expectorated with the regimen of the active cycle of breathing techniques. Other studies looking at the use of high frequency chest compression in people with cystic fibrosis have compared the regimen with that of postural drainage and percussion (Arens *et al* 1994; Warwick & Hansen 1991), but this had been shown to be significantly less effective than the active cycle of breathing techniques over 10 years earlier (Pryor *et al* 1979).

Autogenic drainage was said to be compared with the active cycle of breathing techniques in the study by Miller *et al* (1995), but the regimen originally described was not the active cycle of breathing techniques as used by Pryor *et al* in 1979. Eighteen adolescents and adults with cystic fibrosis (age range: 11-32 years) had entered the study. The paper as submitted for review, for consideration for publication. described a rigid regimen for the active cycle of breathing techniques:

- Tidal volume breathing with the lower chest (breathing control) for 6 breaths
- 3-4 deep inspirations of full capacity
- Breathing control
- 2 forced expirations: the first huff from mid to low lung volume and the second huff at a higher lung volume.

On submission of the paper, one of the reviewers pointed out that the active cycle of breathing techniques was a flexible regimen and not one huff from mid to low lung volume followed by another huff at a higher lung volume. Several huffs to low lung volume, interspersed with breathing control, are often needed before secretions are mobilised from the smaller peripheral airways to the larger airways. It is only when secretions have reached the larger proximal airways that the huff from high lung volume is required. It is a waste of time and effort for the patient to huff from high lung volume when the secretions have not yet reached the proximal airways. When the paper by Miller *et al* was published, the description of the active cycle of breathing techniques had been altered to the description given by this reviewer and read:

- Tidal volume breathing with the lower chest (breathing control) for *approximately* 6 breaths
- 3-4 deep inspirations of full capacity
- Breathing control
- *1 or 2 forced expirations (huffs) from mid to low lung volume*
- *If secretions were felt to be high enough in the proximal airways, a huff was performed at a higher lung volume.*

The paper concluded that peripheral clearance was greater with autogenic drainage, but the two regimens might have been equally effective if, in reality, the huff had been used to mobilise and clear secretions from the more peripheral airways.

The place of thoracic expansion exercises, as a part of the active cycle of breathing techniques, was investigated by White, Stiller & Willson (1997). They studied 15 adults with cystic fibrosis (mean age: 21.8 years). One regimen was the active cycle of breathing techniques with thoracic expansion exercises and the other the active cycle of breathing techniques without thoracic expansion exercises. They found no differences.

in the short term, between the regimens in the measurements of spirometry, sputum weight or oxygen saturation. However comment was made that measurements beyond the scope of the study, for example ventilation, may detect a difference and in conclusion the authors said that further work needs to be undertaken to clarify the long term effects especially in people with hypoxaemia who receive chest clapping or vibrations.

Tucker *et al* (1999) looked at the effect of unilateral breathing exercises, in the sitting position, on regional lung ventilation using Technegas lung ventilation scans in ten physiotherapists, with no history of significant cardiorespiratory disease (mean age: 22.5 years). An increase in relative regional ventilation, on the side of the unilateral thoracic expansion exercise, was observed and this occurred soon after the initiation of inspiration.

The effect of the head-down tilt position was evaluated by Cecins *et al* (1999) in nineteen adult subjects. Thirteen of the subjects had cystic fibrosis, five bronchiectasis of unknown cause and one immotile cilia syndrome (mean age: 37.1 years). There were no significant differences in the wet weight of sputum expectorated or in oxygenation or lung function. The perception of breathlessness, measured using a visual analogue scale, increased significantly following treatment in the head-down tilt position ($p=0.02$). If treatment in the horizontal position makes subjects feel less breathless and in practical terms it is an easier position to adopt, it is likely that the use of this position will increase adherence to treatment.

A mechanical device, Test of Incremental Respiratory Endurance (TIRE), which facilitates repeated maximum inspiratory vital capacity manoeuvres against a fixed

resistance, was initially marketed as an inspiratory training device. This device has been shown to improve inspiratory muscle function when used for eight weeks in people with cystic fibrosis (Enright *et al* 2004). The same device is currently being marketed as a resistive inspiratory manoeuvres (RIM) device for airway clearance, following publication of the study by Chatham *et al* (2004). Twenty adults with cystic fibrosis were randomised to receive, in random order, resistive inspiratory manoeuvres and the active cycle of breathing techniques. There was a two-fold increase in expectoration of sputum with the resistive inspiratory manoeuvres ($p<0.001$).

As the authors state in their conclusion, airway clearance techniques have aimed to increase expiratory flow with resultant high shearing forces to loosen and mobilise excess secretions from the smaller peripheral to the larger more central airways. With the resistive inspiratory manoeuvres method the subject is required to carry out a full inspiratory vital capacity manoeuvre at 80% of maximal pressure, by breathing against a fixed resistance. The maximum pressure is that developed between residual volume and total lung capacity. This increases inspiratory time and the authors hypothesise that resistive inspiratory manoeuvres may increase inspiratory airflow to more peripheral airways with consequent shearing forces acting on airway secretions during the inspiratory phase. This may reduce the need for higher expiratory flows. A reduction in lung volumes with resistive inspiratory manoeuvres, identified by Ionescu *et al* (1998), may alter the positions of the equal pressure points allowing increased movement of more peripherally situated secretions (Chatham *et al* 2004).

Contrary to the Chatham study is the work by Patterson, Bradley & Elborn (2005). These researchers also compared resistive inspiratory manoeuvres with the active cycle of breathing techniques in 20 subjects with bronchiectasis and their results showed an

increase in sputum expectoration with the active cycle of breathing techniques ($p=0.02$). In neither the Chatham *et al* nor Patterson, Bradley & Elborn studies were the effects of the regimens on oxygen saturation or fatigue identified.

Autogenic drainage

Autogenic drainage is breathing at different lung volumes and expiration is used to move the mucus. The aim is to maximise expiratory flow. Breathing at low lung volume level, in the individual patient, is used to mobilise more peripherally situated mucus ('unstick' phase). Breathing around the individual's tidal volume is said to collect mucus in the middle range ('collect' phase) and with breathing around high lung volume, expectoration of secretions from the central airways is promoted ('evacuate' phase) (Figure 2.7). When sufficient mucus has reached the upper airways, it may be cleared by coughing.

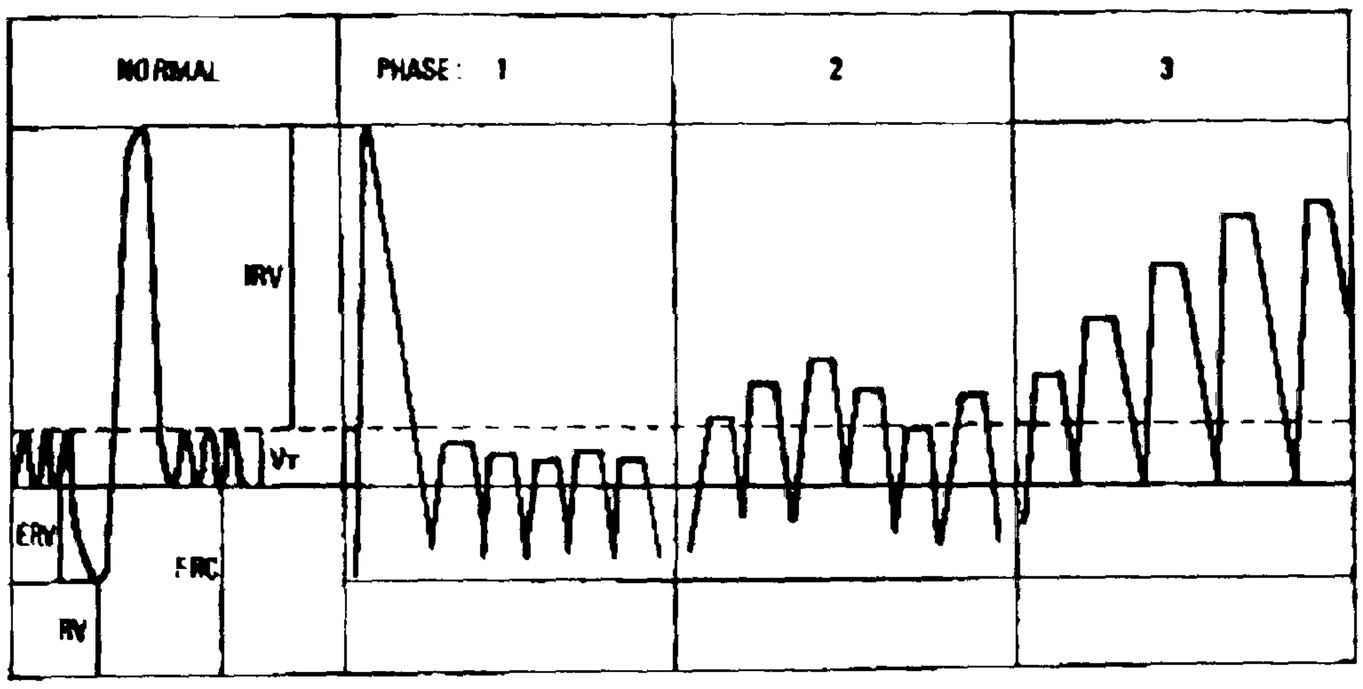


Figure 2.7: The phases of autogenic drainage: Phase 1: Unstick, Phase 2: Collect, Phase 3: Evacuate. From: David 1991. IRV: inspiratory reserve volume, ERV: expiratory reserve volume, RV: residual volume, V_T: tidal volume, FRC: functional residual capacity.

Many of the publications on autogenic drainage are descriptive (David 1991). It was conceived by Jean Chevaillier in Belgium in 1967, but one of the first published papers was by Kraemer *et al* (1986) and in German. Schöni (1989) presented a paper on autogenic drainage at the Royal Society of Medicine and this was published in English. The idea had arisen, in the 1960's, out of concern that postural drainage based on

gravity and coughing, especially in people with asthma, may cause exhaustion, poor expectoration, bronchospasm and even irreversible lung damage. As noted, the regimen required an assistant (Chevaillier 1992). The medical literature was not available electronically and there was no awareness of the paper by Thompson and Thompson (1968), which was in people with asthma.

Chevaillier had observed that mucus clearance increased during breathing exercises, playing, laughing and forced expiratory manoeuvres, and in children during sleep. This appeared to be greater than any increase in clearance with pursed lip breathing, vibration or clapping. Chevaillier's 'new' technique was called autogenic drainage to emphasise that it was a technique which could be undertaken without assistance. The original technique has since been modified by the Germans as they felt that the 'unstick' phase, where the patient breathes into his expiratory reserve volume (Figure 2.7), was difficult for the breathless patient to maintain and the Germans advocated autogenic drainage breaths around tidal volume (Kieselmann 2002).

The autogenic drainage breath begins with inspiration through the nose. At the end of inspiration and with the glottis open, the patient holds his breath for two to three seconds to encourage optimal filling via collateral airways. This 'hold' is said to facilitate more equal filling of lung segments by allowing for the variation in time constants within different lung regions (Chevaillier 1992). Expiration is performed through the open glottis and open mouth, without pursed lips, as if sighing. The expiratory force is balanced to obtain the highest possible airflow without causing airway compression. This is to encourage narrowing, but not compression, of the airway lumen and consequent increase in the speed of airflow.

In the 'unstick' phase, tidal breathing is lowered into the normal expiratory reserve volume to encourage movement of mucus from the smaller more peripheral airways by the increase in airflow during expiration. Tidal volume breathing is gradually brought up into the inspiratory reserve volume, the 'collect' phase, and it is said that the longer the expiratory time, the greater the distance the mucus will be transported (Chevaillier 1992). Coughing is discouraged throughout these two stages. Finally, from the middle of the inspiratory reserve volume, the 'evacuate' phase, the patient increases expiratory flow and gentle coughing is used to clear the mucus. It is accepted that this technique takes concentration to perform effectively and it may take longer to learn than the active cycle of breathing techniques (Miller *et al* 1995).

Miller *et al* (1995) compared autogenic drainage with the active cycle of breathing techniques. There is evidence that it was not the active cycle of breathing techniques which was used in this study (Webber 1995), but the study demonstrated that in 18 patients (adolescents and adults) with cystic fibrosis (age range: 11-32 years) autogenic drainage is effective in augmenting the movement and expectoration of excess bronchial secretions. The results showed no deterioration in oxygen saturation during or after treatment, no clinically significant change in heart rate and no statistically significant difference in lung function although there was a trend towards an improvement in forced expiratory flow from 25-75% (FEF_{25-75}). The weight of sputum expectorated, during the 30-minute treatment and for up to one hour after treatment, ranged from 2 to 105 grams. Using radio-labelled aerosol, clearance was demonstrated from both central and peripheral lung regions.

Giles *et al* (1995) compared the short term effects of postural drainage and clapping ('conventional' postural drainage) with autogenic drainage in 10 adolescents and adults

with cystic fibrosis. The outcome measures were oxygen saturation. pulmonary function and sputum expectoration. The results showed no significant differences in pulmonary function or sputum expectorated. Oxygen saturation fell during the postural drainage treatment ($p<0.01$) but had returned to pre-treatment values 15 minutes later. With autogenic drainage, oxygen saturation increased during treatment ($p<0.01$) and this was maintained 60 minutes following treatment. The authors concluded that postural drainage and autogenic drainage have similar short term benefits, but the improvement in oxygen saturation with autogenic drainage may be advantageous in older patients with worsening oxygenation.

This paper (Giles *et al* 1995) demonstrates the influence the Reisman study (Reisman *et al* 1988) had on the direction of airway clearance in the United States. The study quotes Reisman *et al* (1998) as evidence for postural drainage and clapping as the 'gold' standard in enhancing mucus clearance, but that it required assistance from another person which was inconvenient for adolescent and adult patients. Autogenic drainage was described as a technique which would allow patients to do their own therapy, providing more independence and control for the individual.

The viscoelasticity of sputum was examined by App *et al* (1998) in 14 people with cystic fibrosis (age range: 7-41 years). Subjects were randomised to either autogenic drainage or the flutter. Before and after four weeks of treatment, forced expiratory volume in one second (FEV_1) forced vital capacity (FVC), sputum volume and sputum viscosity were measured. Following a one-week washout period, the subjects crossed over to the alternative regimen. There were no significant differences between the regimens in pulmonary function or sputum volume, but sputum viscoelasticity (rigidity

index) was significantly lower following the flutter regimen ($p<0.01$), when compared with the autogenic drainage regimen.

McIlwaine *et al* (1991) looked at the effect on oxygen saturation of postural drainage ('conventional') and autogenic drainage, in single treatment sessions (30 patients, age range: 12-19 years). With postural drainage there was a mean drop in oxygen saturation and with autogenic drainage, a mean gain. This was significant ($p=0.002$).

The same group went on to study the long term effects of the two regimens (postural drainage and autogenic drainage) (Davidson *et al* 1992). At the end of one year both groups demonstrated improvements in lung function (FVC, FEV_1, FEF_{25-75}), but there was no significant difference between the two groups. It was intended that the subjects would cross over in the second year, but some subjects randomised to autogenic drainage in the first year did not wish to cross over to their old regimen of postural drainage and some who agreed to cross over, augmented postural drainage with autogenic drainage techniques. Postural drainage had required an assistant and autogenic drainage offered independence.

Cornet

The R-C Cornet® is a curved plastic tube containing a flexible, latex-free valve hose (Figure 2.8). During expiration through the cornet, a positive expiratory pressure and an oscillatory vibration of the air within the airways is generated. It can be used in any position, as it is independent of gravitational forces. The flow, pressure and frequency of the oscillations can be adjusted, by twisting the mouthpiece (inserted in the curved tube), to suit the individual patient. Coughing or huffing clears secretions mobilised to the central airways.

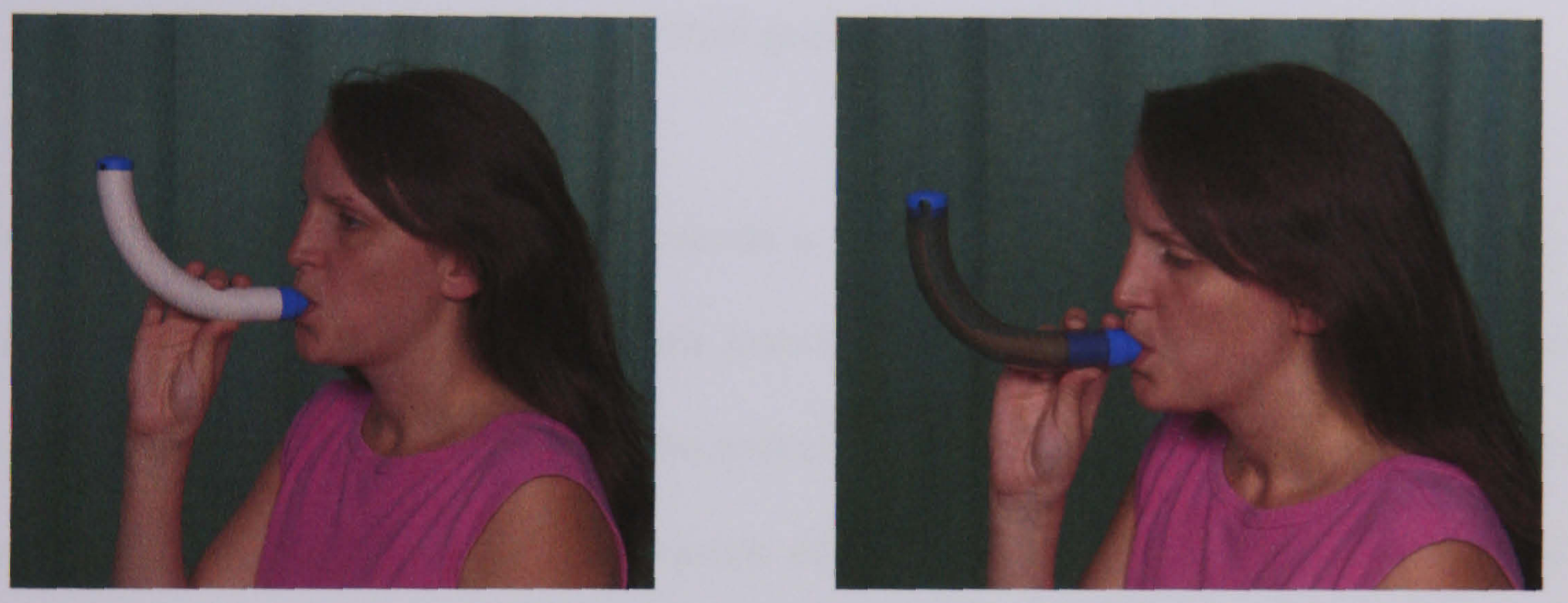


Figure 2.8: The cornet. The right hand picture shows the inner tube beginning to inflate in a 'see through' demonstration device.

Much of the literature on the RC-Cornet® (cornet) has been published in the Journal *Pneumologie* and is written in German, but English translations are available. The cornet is a development of an oscillating positive expiratory pressure device designed by Professor Ulrich Cegla of Germany. The majority of the studies, using the cornet, have to date been undertaken in people with chronic obstructive airways disease, but the cornet like the flutter (p.71) is an oscillating positive pressure device and the flutter has

been extensively studied in people with cystic fibrosis. The cornet has the advantage of being position independent and the pre-set pressure and flow through the device can be altered.

In 1997 Cegla *et al* studied 90 patients (mean age 56 years) with chronic obstructive pulmonary disease.

The subjects were randomised to one of three groups:

1. Medical management (e.g. prednisolone, theophylline, β_2 sympathomimetic) and the airway clearance regimen of the flutter
2. Medical management and the airway clearance regimen of the cornet
3. Medical management only (control group).

Use of the cornet showed a trend towards a reduction in residual volume when pre-treatment values were compared with post-treatment values. Possible physiological reasons for this were not discussed. The reduction in residual volume was not seen with the flutter regimen. The partial pressure of carbon dioxide in arterial blood was significantly reduced by both regimens (The cornet: $p<0.05$ on day 1, $p<0.0001$ on day 4, $p<0.0001$ on day 7 and the flutter: $p<0.001$ on day 1, $p<0.00001$ on day 4, $p<0.00001$ on day 7). There were no significant changes in the control group. The patients' subjective assessment of sputum and well-being was said to be 'significantly better' using the cornet and there was a trend towards a reduction in coughing.

In 2002 Cegla *et al* published the results of a long term study (2 years) in people with chronic obstructive pulmonary disease. Fifty patients (mean age 63.4 years) were randomised to either drug therapy alone or drug therapy and physical therapy in the form of the cornet. Thoracic gas volume (percent of normal) and airway resistance

decreased significantly with inclusion of the cornet in the treatment regimen (thoracic gas volume: $p<0.02$, airway resistance: $p<0.02$). Vital capacity increased in the cornet group ($p<0.02$). Fewer patients using the cornet required antibiotics over the period ($p<0.001$) and there was a reduced need for hospital care ($p<0.001$).

Nakamura *et al* (1998) studied the effects of the cornet and flutter on the cohesiveness and viscoelasticity of sputum from patients with bronchiectasis. This *in vitro* study demonstrated a non-significant decrease in cohesiveness at 15 minutes with the flutter and a significant decrease at 30 minutes ($p=0.039$). With the cornet there were significant decreases at both 15 ($p=0.034$) and 30 minutes ($p=0.006$). It was concluded that both devices should facilitate airway clearance.

Cohesiveness and viscoelasticity had also been studied, in the short term (a 15-minute treatment session), in 10 patients with bronchiectasis (mean age 46.7 years) (Feng *et al* 1998). The use of the cornet decreased the viscoelasticity ($p=0.024$) and cohesiveness ($p=0.013$) of sputum and increased forced vital capacity ($p=0.026$), but there was said to be no correlation between pulmonary function and sputum rheology.

Care must be taken in extrapolating these results to people with cystic fibrosis, but the studies are an indication that the cornet is likely to be an effective airway clearance regimen in people with cystic fibrosis.

Flutter

The flutter is a pipe-shaped device with a high-density stainless steel ball enclosed in a cone in the bowl of the 'pipe' (Figures 2.9 & 2.10). During expiration through the flutter, the rise and fall of the ball and its movement along the surface of the cone create a positive expiratory pressure and oscillatory vibration of the air within the airways. In addition, the same ball movements produce intermittent airflow accelerations. These three phenomena help to loosen secretions that are then mobilised to the central airways and cleared by deep exhalations through the device with the aid of coughing and huffing.



Figure 2.9: The flutter.

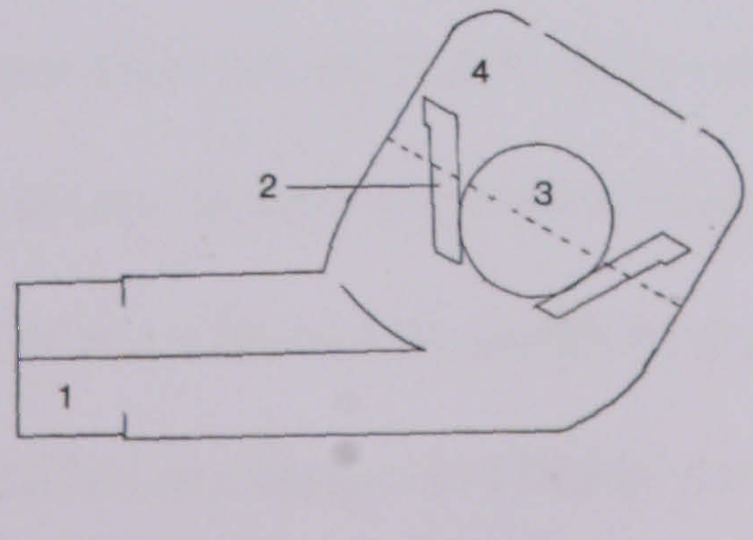


Figure 2.10: Components of the flutter. 1; mouthpiece 2; cone 3; stainless steel ball 4; protective coating with holes.

The definitive study on the flutter is said to be that by Konstan *et al* (1994). They studied 18 patients with cystic fibrosis (age range: 8-38 years). Three treatment regimens were compared:

1. Cough: vigorous voluntary coughing every two minutes for 15 minutes.
2. Postural drainage: one minute of chest percussion by a respiratory therapist followed by five forced pursed-lip expirations with manual vibrations by the therapist. Voluntary coughing and expectoration were then encouraged. This sequence was carried out in up to 10 positions for 15 minutes.
3. Flutter: exhalation through the flutter was encouraged until coughing and expectoration were 'precipitated'.

A significantly greater amount of sputum ($p<0.001$), the only outcome measure, was expectorated with the flutter regimen. There were no differences between cough and postural drainage. The authors concluded that the flutter was more effective than conventional techniques in clearing mucus from the airways. It was said to be simple and safe to use and it was predicted that it would improve adherence to treatment.

It is interesting to note that this paper lists only seven references. Five of these are from the United States of America, where this study was undertaken. The remaining two are references, from Germany, relating to the flutter. The paper was published in 1994 and the study protocol would have been set up two to three years earlier. Available in the literature, to use as the control arm instead of postural drainage, was the active cycle of breathing techniques (Pryor *et al* 1979) and the positive expiratory pressure mask (Falk *et al* 1984). These studies had led to changes in clinical practice from postural drainage and percussion to regimens which were more effective in terms of airway clearance and could be undertaken independent of an assistant.

Two years before publication of the study by Konstan *et al* (1994). Lindemann (1992) had compared the flutter with autogenic drainage, but this work was published in *Pneumologie* and in German. Twenty patients with cystic fibrosis (age range: 7 – 28 years) were randomly allocated to the flutter and to autogenic drainage, each patient acting as his own control. The primary outcome measure was weight of sputum expectorated and it was concluded that the flutter was at least equal to autogenic drainage. It is important to note that the flutter regimen as used in this study included huffing as described by Pryor *et al* (1979).

A study by Lyons *et al* was also published in 1992. There were four arms to this study:

1. Physiotherapy using the active cycle of breathing techniques
2. Flutter only
3. Flutter and physiotherapy
4. Sham flutter and physiotherapy.

There was a statistically significant difference with the flutter only regimen in the amount of sputum expectorated (p=0.015). Less sputum was cleared. The conclusion was that the flutter could not be substituted for physiotherapy using the active cycle of breathing techniques. Huffing was not included in the flutter regimen.

Published in the same year as the study by Konstan *et al* (1994) was a study by Pryor *et al* (1994). Pryor *et al* compared the flutter as used by Konstan *et al* with the active cycle of breathing techniques. Twenty-four adults with cystic fibrosis participated (mean age: 24.4 years). They were randomised to either the active cycle of breathing techniques or to 10 minutes of the flutter followed by the active cycle of breathing techniques. For ethical reasons the active cycle of breathing techniques followed treatment with the flutter, in the flutter regimen. Of concern was the effectiveness of the flutter as an

airway clearance regimen on its own. If the flutter alone was more effective than the active cycle of breathing techniques, the combined regimen would have been superior.

The mean weight of sputum expectorated during a treatment session using the active cycle of breathing techniques was 21.2 grams (range 1.4 - 49.6 grams). For the regimen using the flutter it was 16.6 grams (range 0.6 – 47.5 grams) (Figure 2.11). This study demonstrated that less sputum was expectorated during treatment when the flutter was included in the regimen. The authors concluded that no advantage could be identified by inclusion of the flutter and the possibility of sputum retention, during the use of the flutter, was of concern. The flutter was used as recommended by the Swiss proponents of the device (VarioRaw SA). The subject breathed around tidal volume and expiration was out through the flutter. No forced expiratory manoeuvre was included during this part of the regimen.

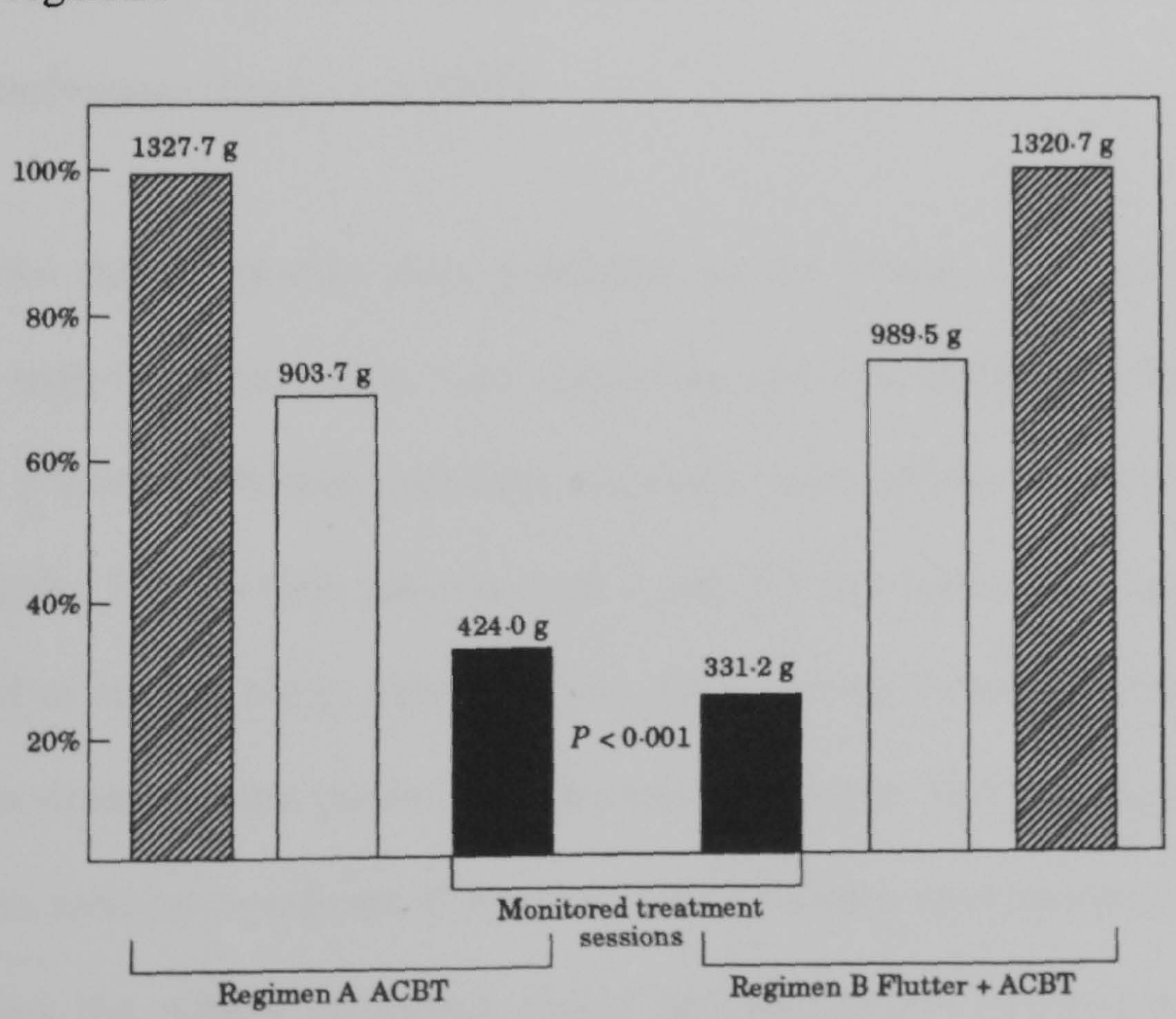


Figure 2.11: Active cycle of breathing techniques versus flutter. Weight of sputum expectorated From: Pryor *et al* (1994). The black bars show the amount of sputum expectorated during the monitored treatment sessions. The white bars represent the amount of sputum expectorated in between the monitored treatment sessions and the hatched bars show the total amount of sputum expectorated in a twenty-four hour period.

Four years later Homnick, Anderson, & Marks (1998) compared the flutter to 'standard' chest physiotherapy in 22 patients with cystic fibrosis (age range: 8 – 44 years). The regimens were 'flutter therapy' or 'standard manual chest physical therapy' four times a day during a hospital admission. Standard physical therapy required assistance from a respiratory therapist. The duration of a flutter session averaged 15 minutes and standard physical therapy approximately 30 minutes. Patients were randomised to one or other regimen and all improved during admission to hospital, but there were no detectable differences between either of the regimens.

The authors (Homnick, Anderson & Marks 1998) stated that standard manual chest percussion has been the 'gold standard' for airway clearance for decades. They did however acknowledge that, in addition to the flutter, there were other airway clearance regimens which can be 'independently administered' and quoted the active cycle of breathing techniques (Pryor *et al* 1994).

In 2001 two further studies were published on the flutter. Oermann *et al* (2001) compared high-frequency chest wall oscillation and the flutter (oscillating positive expiratory pressure). Primary outcome measures were spirometry and lung volume measurements. Twenty-nine subjects with cystic fibrosis entered the study and were randomised to receive either chest wall oscillation or the flutter, for four weeks, and after a two-week washout period, the alternative regimen. The age range was 9 – 39 years. There were no significant differences. in the primary outcome measures, between the regimens but patient preference varied and the authors commented that patient satisfaction and preference should be considered when prescribing home therapy.

McIlwaine *et al* (2001) compared the flutter with positive expiratory pressure over a period of one year. Forty children (age range: 7 – 16 years) entered the study and were randomised to receive either the positive expiratory pressure mask or the flutter for one year. There were significantly greater rates of decline in the flutter group in FVC ($p=0.05$) with a similar trend in FEV_1. There was also a significant decline in Huang scores ($p=0.05$) with the flutter and increased hospitalisations ($p=0.03$). Admission to hospital tended to occur seven to nine months into the study but the rate of adherence to treatment, as recorded by the patients, was similar in both groups. The authors concluded that the flutter was not as effective as the positive expiratory pressure mask in this group of patients. McIlwaine *et al* hypothesised that the differences between the two regimens may be a consequence of the continuation of expiration into the expiratory reserve volume with the flutter. This they said was likely to be within closing volume, with consequent airway closure. With the positive expiratory pressure regimen, end expiration is above resting lung volume. Owing to the outcome of this study, the Cystic Fibrosis Clinic at the British Columbia Children's Hospital discontinued using the flutter.

Both McIlwaine *et al* (2001) and Konstan *et al* (1994) used the same flutter regimen:

> '...the subject exhaled through the flutter device until coughing was precipitated and then expectorated as much sputum as possible.' (Konstan *et al* 1994).

Pike *et al* (1999) repeated the study by Pryor *et al* (1994), but with the inclusion of a forced expiratory manoeuvre during the flutter regimen. A regimen of the flutter and the forced expiratory manoeuvre of huffing combined with breathing control (the forced expiration technique) was compared with the active cycle of breathing techniques.

Twenty-one patients with cystic fibrosis (median age: 26 years) participated in the study, a one day cross-over study. Both regimens were comparable with no detectable differences among the outcome measures of sputum weight, spirometry or oxygen saturation but there were significant increases, with both regimens, when after treatment FEV_1 and FVC were compared with before treatment values.

As discussed in the section on autogenic drainage, App *et al* (1998) looked at the viscoelasticity of sputum in 14 people with cystic fibrosis (age range: 7-41 years) after randomisation to either the flutter or autogenic drainage. Sputum viscoelasticity (rigidity index) was significantly lower following the flutter regimen ($p<0.01$) when compared with the autogenic drainage regimen. The mucociliary clearability index (MCI) and cough clearability index (CCI) were calculated from the results of viscoelasticity (App *et al* 1998). These results are graphically demonstrated in Figure 2.12. Both mucociliary clearability and cough clearability were increased with the flutter.

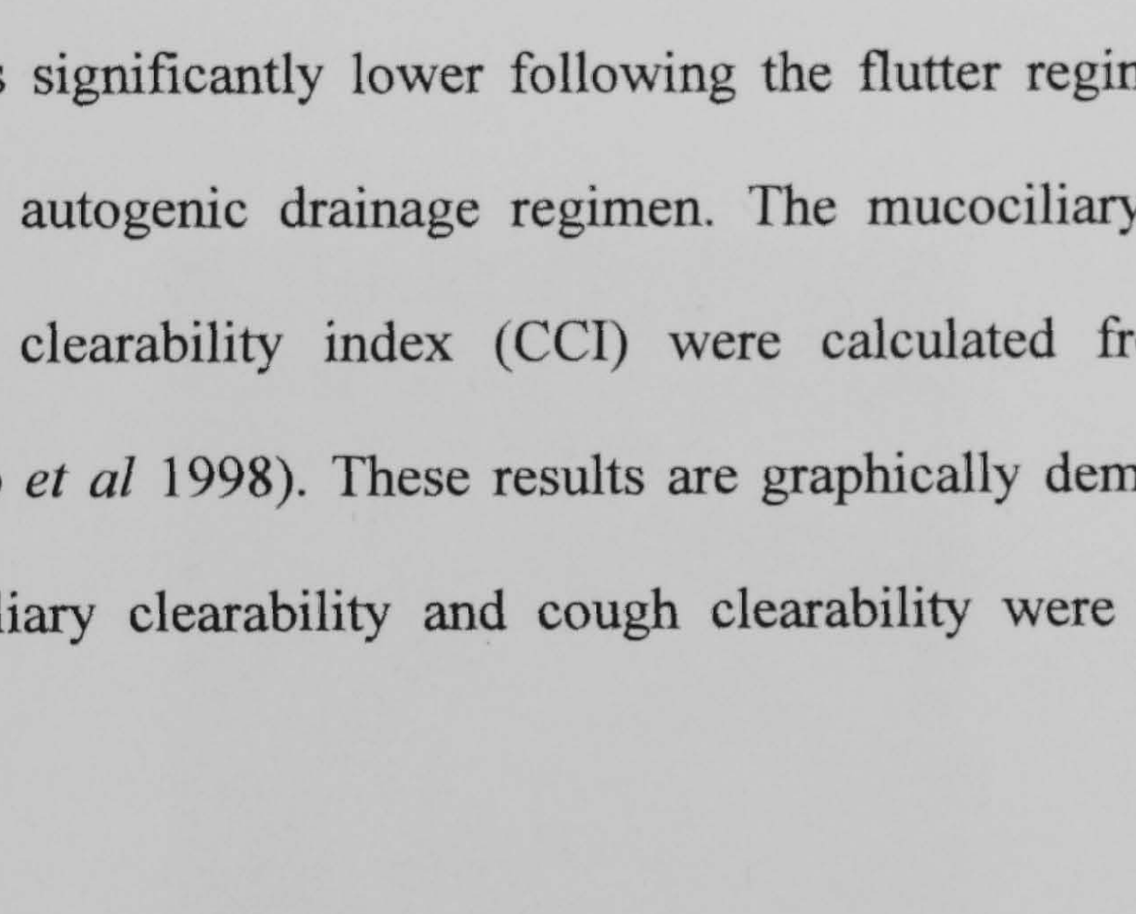


Figure 2.12: The mucociliary clearability index (MCI) and cough clearability index (CCI) for autogenic drainage (AD) and for the flutter. From: App *et al* 1998.

Positive expiratory pressure

The positive expiratory pressure (PEP) device consists of a facemask or mouthpiece and a one-way valve to which expiratory resistors can be attached (Figures 2.13 and 2.14). Tidal breathing, with a slightly active expiration, is used and the lung volume is kept up by avoiding complete expiration. The diameter of the resistor is determined for each patient to give a steady resistance of between 10 and 20 centimetres of water in mid-expiration. The forced expiration technique is used to clear the secretions which have been mobilised.



Figure 2.13: The positive expiratory pressure mask showing one-way valve with resistor on the expiratory arm and manometer to measure the expiratory pressure.

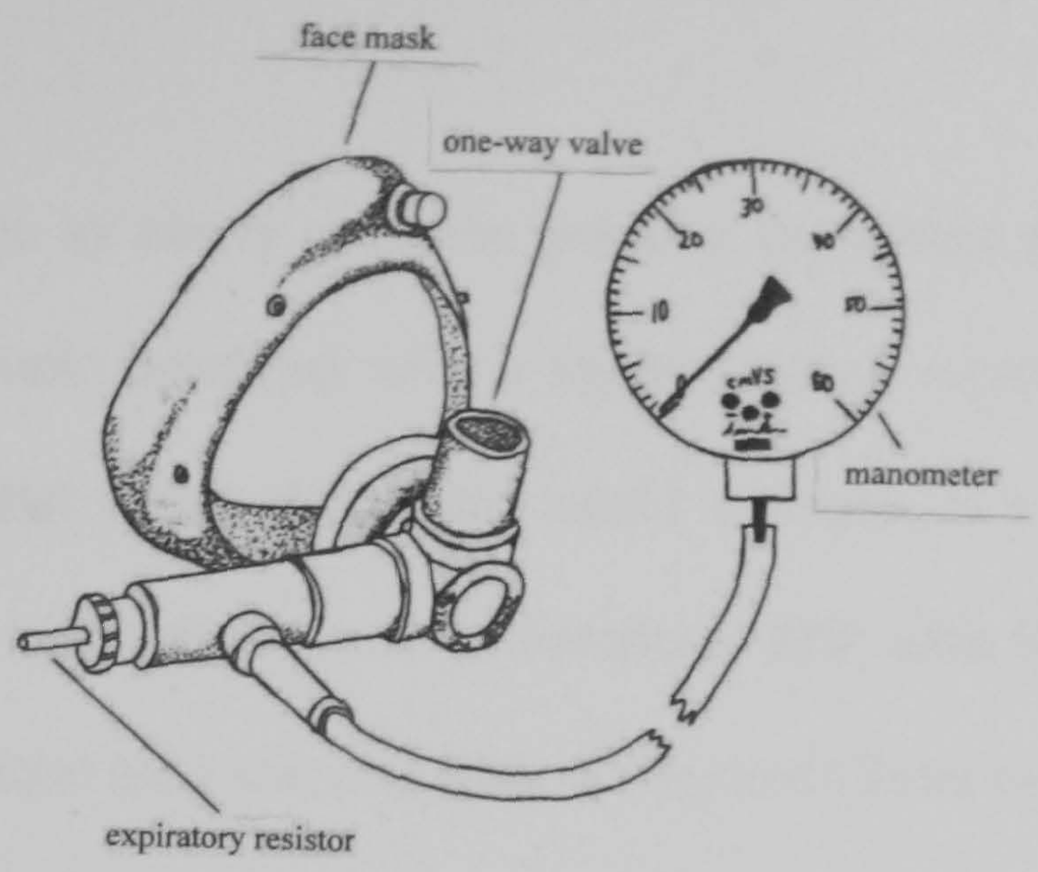


Figure 2.14: The components of the positive expiratory pressure mask system – face mask, one-way valve, expiratory resistor and manometer.

The definitive paper on the positive expiratory pressure mask is from Denmark by Falk *et al* (1984). This study revolutionised airway clearance in Denmark and to this day the positive expiratory pressure mask (PEP) is the only airway clearance technique practised in Denmark.

The Danes studied 14 people with cystic fibrosis (age range: 14 – 30 years) and each patient was assessed using each of four regimens:

I. Postural drainage in seven different positions:
   - four for the lower lobes with the foot of the bed elevated 30 degrees
   - one for the middle lobe with the foot of the bed elevated 30 degrees
   - two in the sitting position for the upper lobes.

The order of the positions was always the same and each position was maintained for four to five minutes (Total time 35 minutes). The forced expiration technique (sic), consisting of forced expirations with the glottis open from midway between functional residual capacity and total lung capacity to midway between functional

residual capacity and residual volume, was included.

II. Postural drainage as above with the positive expiratory pressure (PEP) mask using diaphragmatic breathing with a slightly active expiration. The expiratory resistance was that which the patient could maintain at a steady PEP for two minutes without exhaustion. Six to 12 breaths of PEP were followed by the forced expiration technique (sic) and coughing as required (Total time 35 minutes).

III. Positive expiratory pressure (PEP) in the sitting position. Six to 12 breaths of PEP were followed by the forced expiration technique (sic) and coughing as required (Total time 20 minutes).

IV. Pursed lip breathing with a slow diaphragmatic inspiration and expiration through pursed lips for five to eight breaths, followed by the forced expiration technique (sic) and coughing as required. The sitting position was used (Total time 20 minutes).

Differences among the regimens were reflected in:

a) Forced vital capacity (FVC). Following Treatment I, intended to be postural drainage using the forced expiration technique, there was a 6.6 % reduction in FVC ($p<0.01$). Following Treatment III, positive expiratory pressure in the sitting position, there was a 4.7% increase in FVC ($p<0.01$).

b) Weight of sputum expectorated. Treatments II, III and IV led to the expectoration of significantly more sputum than I ($p<0.01$).

c) Skin oxygen tension. The time (minutes) spent below the pre-treatment value was significantly greater with Treatment I when compared with Treatments II. III, and IV ($p<0.01$) and the percent change was significantly greater ($p<0.01$).

It was therefore appropriate that the Danes changed their airway clearance practice to that of Treatment III, the positive expiratory pressure mask in sitting and this was the regimen preferred by 11 of the 14 subjects on the study. The expiratory resistor for the mask, in this group of patients, was that with a diameter of 3.0 or 3.5 millimetres. This produced a positive expiratory pressure of approximately 17 centimetres of water in mid-expiration.

It was unfortunate that what was called the forced expiration technique was not the regimen described by the proponents of the regimen (Pryor *et al* 1979). With the use of seven different postural drainage positions in a thirty-five minute session it is not surprising that oxygen tension fell, as this regimen would loosen and mobilise secretions from the different areas of the lungs but there would not be time for adequate clearance of excess secretions with only four to five minutes in each position. Huffing without the pauses for breathing control, as used in this study, may increase airflow obstruction. This has never been recommended and is not the forced expiration technique. The difference in time between regimens I & II and III & IV is a reduction of 43% for regimens III & IV and a saving of 15 minutes per treatment session. This is an important factor in any airway clearance regimen especially in the management of a chronic condition.

Hofmeyr, Webber & Hodson (1986) studied the airway clearance technique of positive expiratory pressure after the Lead Researcher had spent time with the Danish group.

The English group had three arms to their study:

A. A cycle of four deep inspirations with a relaxed expiration, a period of breathing control (relaxed gentle abdominal breathing) and the forced expiration technique (one or two huffs combined with breathing control). This was undertaken in gravity assisted positions.

B. A cycle of six breaths with the positive expiratory pressure mask, breathing control and the forced expiration technique in gravity assisted positions.

C. A cycle of six breaths with the positive expiratory pressure mask, breathing control and the forced expiration technique in the sitting position.

The mean weight of sputum expectorated (SEM) during treatment sessions in a twenty-four hour period, for Treatment A, was 63.3 (9.16) grams. For Treatment B it was 54.5 (9.72) grams and for Treatment C, 42.3 (5.12) grams. Treatment A produced significantly more sputum than Treatment B ($p<0.025$) and Treatment C ($p<0.001$). Treatment B produced more sputum than Treatment C ($p<0.005$).

As a consequence of this study the English group did not change clinical practice and continued with postural drainage using the forced expiration technique, the active cycle of breathing techniques. Following discussions with the Danish group, huffing became combined with breathing control - the forced expiration technique - as a part of the positive expiratory pressure airway clearance regimen used in Denmark.

Mortensen *et al* (1991), from Denmark, studied the effects of the regimens of:

(a) positive expiratory pressure and the forced expiration technique in the sitting position

(b) postural drainage and the forced expiration technique

(c) control with the subject resting in the sitting position, on whole lung and regional tracheobronchial clearance in 10 patients with cystic fibrosis. The forced expiration technique was that as described by Hofmeyr, Webber & Hodson (1986). The researchers had noted, from the study by Hofmeyr, Webber & Hodson, the outcome of more sputum expectorated with postural drainage and the forced expiration technique, but felt that the non-invasive radioaerosol technique involving inhalation of radioaerosol may provide a more reliable evaluation of the effect of chest physiotherapy on mucus clearance. They were also interested in looking at the usefulness of weight of sputum as an index of tracheobronchial clearance.

Mucus clearance from both central and peripheral lung regions was greater with both treatment regimens than with the control. They found that the thoracic expansion exercises and postural drainage resulted in mucus clearance, from the lower lobe, which was similar to the mucus clearance by tidal breathing with positive expiratory pressure in the upright position when both regimens were used with the forced expiration technique. The results showed a poor correlation between radioaerosol clearance and sputum weight. The authors discuss the limitations of radioaerosol measurements as an outcome measure, but conclude that radioaerosol measurements should be preferred.

This study (Mortensen *et al* 1991) demonstrates correlation between studies when the same regimen is used in practice. Regimens unique to researchers have masqueraded under the umbrella of the active cycle of breathing techniques. The regimen of postural drainage and the forced expiration technique as used by Mortensen *et al* was the active cycle of breathing techniques and with only two positions, rather than seven, used in a treatment session. The regimen of positive expiratory pressure and the forced expiration technique was that of the forced expiration technique with huffing combined with

periods of breathing control.

The result that both treatment regimens were equally effective in terms of mucus clearance may be real rather than conflicting. Several years had passed since the studies by Falk *et al* (1984) and Hofmeyr, Webber & Hodson (1986) had been undertaken. During this time there were significant improvements in the medical management of people with cystic fibrosis, especially in the areas of nutrition and the long term effects of the use of inhaled antibiotics. It would have been a different population from that published in 1984 and 1986 and perhaps a preview of the decreasing significance of the effect of gravity in the presence of effective airway clearance techniques.

Steen *et al* (1991) acknowledged that postural drainage using the forced expiratory technique (sic) had improved the efficiency of chest physiotherapy in addition to offering independence, but had wondered if positive expiratory pressure together with the forced expiration technique would obviate the need for gravity assisted positions. Earlier work by Tyrrell, Hiller & Martin (1986) voiced concern that the positive expiratory pressure mask alone, that is without the forced expiration technique, was not as effective as conventional physiotherapy. The patients in the Steen *et al* study were younger than those in the Hofmeyr, Webber & Hodson study, and were not expectorating the copious amounts of sputum (at least 20 grams in twenty-four hours) of the subjects in the study by Hofmeyr, Webber & Hodson. It was therefore felt that positive expiratory pressure in sitting, together with the forced expiration technique, may offer an effective alternative for these people.

Twenty-eight patients with cystic fibrosis entered the study (age range: 8 – 22 years) and were randomly allocated to one month of one of four regimens: postural drainage

with the forced expiration technique, five minutes of positive expiratory pressure followed by postural drainage, positive expiratory pressure alone in the sitting position and positive expiratory pressure with the forced expiration technique in the sitting position. Subjects crossed over to the other regimens without a washout period. There were no significant differences as measured by Shwachman score, Chrispin-Norman score or pulmonary function tests. On completion of the study, 23 of the subjects indicated that they would include positive expiratory pressure in their airway clearance regimen and many appreciated the independence. In retrospect this is another study indicating that with less sputum use of the head-down tipped position may not be of clinical significance.

In the same year van der Schans *et al* (1991) studied lung volumes and mucus clearance by positive expiratory pressure and by coughing, using radioactive aerosol tracer. In eight patients with cystic fibrosis, positive expiratory pressure breathing increased lung volumes but did not on its own lead to an improvement in mucus transport. The forced expiration technique had not been included.

Denmark and the United Kingdom changed clinical practice as a consequence of their independent airway clearance studies. Denmark changed to positive expiratory pressure and the United Kingdom changed to the active cycle of breathing techniques, but the studies were short term. These studies did not immediately influence practice in either Canada or in the United States of America.

At a later date the North Americans were willing to compare positive expiratory pressure with postural drainage and percussion, in the long term, in recognition of the short term studies including those by (Falk *et al* 1984; Hofmeyr, Webber, & Hodson

1986; Steen *et al* 1991; Tyrrell, Hiller, & Martin 1986). It was recognised that postural drainage and percussion required a comparatively longer time for treatment, needed an assistant and many experienced physical discomfort from the chest percussion and chest vibration during the session. The indications were that the positive expiratory pressure technique may take less time, it was independent of an assistant and did not include either chest percussion or vibration.

McIlwaine *et al* (1997) studied 40 patients with cystic fibrosis (age range 6 – 17 years, mean: 10.1 years) for a period of one year. They were randomised either to positive expiratory pressure in the sitting position or conventional postural drainage and percussion. The latter regimen was said to be 'standard practice' in North American Cystic Fibrosis Centres at the time. It included deep breathing, vibration and cough. Forced expirations were used. There is no mention of breathing control with the forced expirations in the postural drainage arm, but it is mentioned in the positive expiratory pressure arm. The regimen, which describes the use of five or six positions for three to five minutes in a 30-minute session, was based on the Danish study of 1984 published 13 years earlier.

The positive expiratory pressure group demonstrated an improvement in FEV_1 and FVC which was significantly greater than the decline in both FEV_1 and FVC seen in the postural drainage group. For FEV_1 $p=0.02$ and for FVC $p=0.04$. The subjects on the positive expiratory pressure arm preferred this regimen to that of postural drainage which they had been using before entering the study. The authors concluded that positive expiratory pressure was a superior form of airway clearance for people with cystic fibrosis and should be considered an important advance.

A second group from North America (Gaskin *et al* 1998) also compared conventional postural drainage and percussion with positive expiratory pressure and over a period of two years, but in an older group of patients compared with McIlwaine *et al* (1997). Sixty-six patients with cystic fibrosis (age range: 11- 45 years, mean: 21.6 years) entered the study. Over the two-year period there were no significant differences either in the rate of decline in FEV_1 between the two groups or in the Quality of Well Being scores.

More recently Darbee *et al* (2004) studied the ventilation distribution and gas mixing with positive expiratory pressure breathing in five adults and adolescents with cystic fibrosis and moderate to severe lung disease. The results demonstrated improved gas mixing associated with improvements in lung function, sputum expectoration and oxygen saturation.

High pressure positive expiratory pressure is a modified form of positive expiratory pressure which has been studied by the Austrians (Oberwaldner, Evans, & Zach 1986). The pressures used are between 50 and 120 centimetres of water and this has been shown to be an effective airway clearance technique in the treatment of people with cystic fibrosis (Oberwaldner, Evans, & Zach 1986; Pfleger *et al* 1992). This regimen, of high pressure positive expiratory pressure, was not considered for the study of this thesis as very close and ongoing monitoring, using flow volume loops is required.

Chapter III. Physiology of Airway Clearance Techniques

'The mucociliary escalator is one of the primary innate defence mechanisms of the lung, playing a central role in pulmonary health. It consists of two intrinsically linked components: the ciliated epithelium and the airway surface liquid (ASL); the combined function of which is efficient removal of foreign material and cellular debris from the lungs' (McShane *et al* 2004).

The following scanning electron micrograph of ciliated epithelial cells beating in the fluid layer beneath the mucus (Figure 3.1) depicts the efficiency of the mucociliary clearance mechanism of the lung, in the absence of disease or infection.



Figure 3.1: Scanning electron micrograph of ciliated epithelial cells beating in the fluid layer beneath the mucus (Mu). From: Jeffery 1995.

Bronchial secretions are said to move by three mechanisms (Lapin 2002; Selsby & Jones 1990).

1. 'Slug flow' - the means by which a semi-solid mucus plug, obstructing or partially obstructing an airway, can be pushed from behind by airflow.
2. 'Annular flow' - the movement of mucus along the walls of the airway, either by being pulled along by expiratory flow or transported by cilia.

3. 'Mist flow' - aerolised mucus which is exhaled as suspended droplets.

Mucus is thixotropic, that is the viscosity of mucus will decrease when exposed to high sheer forces. The airway narrowing during a forced expiratory manoeuvre, cough or huff, will produce rapid air flow which will reduce mucus viscoscity and aid the clearance of mucus by annular and mist flow. 'Slug' and 'annular' airflow are said to account for the majority of airway clearance (Lapin 2002). Airflow is therefore essential for airway clearance.

Forced expiratory manoeuvres

'Forced expiratory manoeuvres are probably the most effective part of chest physiotherapy' (van der Schans 1997). The forced expiratory manoeuvre may be either a huff or a cough. With both, the level within the airways from which an individual huff or cough will be effective in airway clearance is dependent on lung volume. This can be explained using the concept of the equal pressure point (West 1997).

The equal pressure point (EPP) is the point where the pressure within the airway is equal to the pressure surrounding the airway (Figure 3.2). The airway upstream of the equal pressure point, towards the alveoli, is distended and the airway downstream is compressed. This dynamic compression is an important mechanism which determines the efficiency of cough (Macklem 1974).

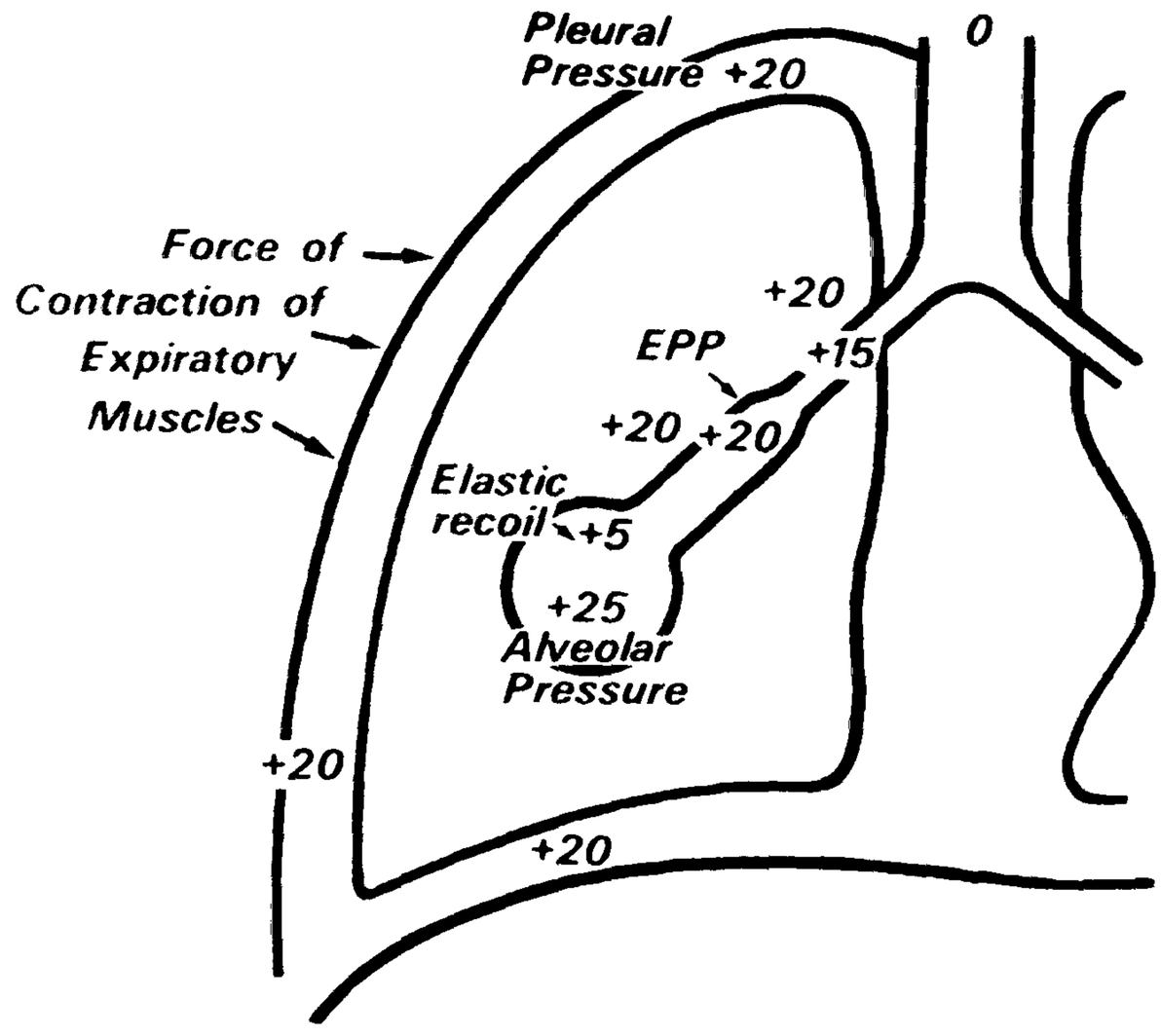


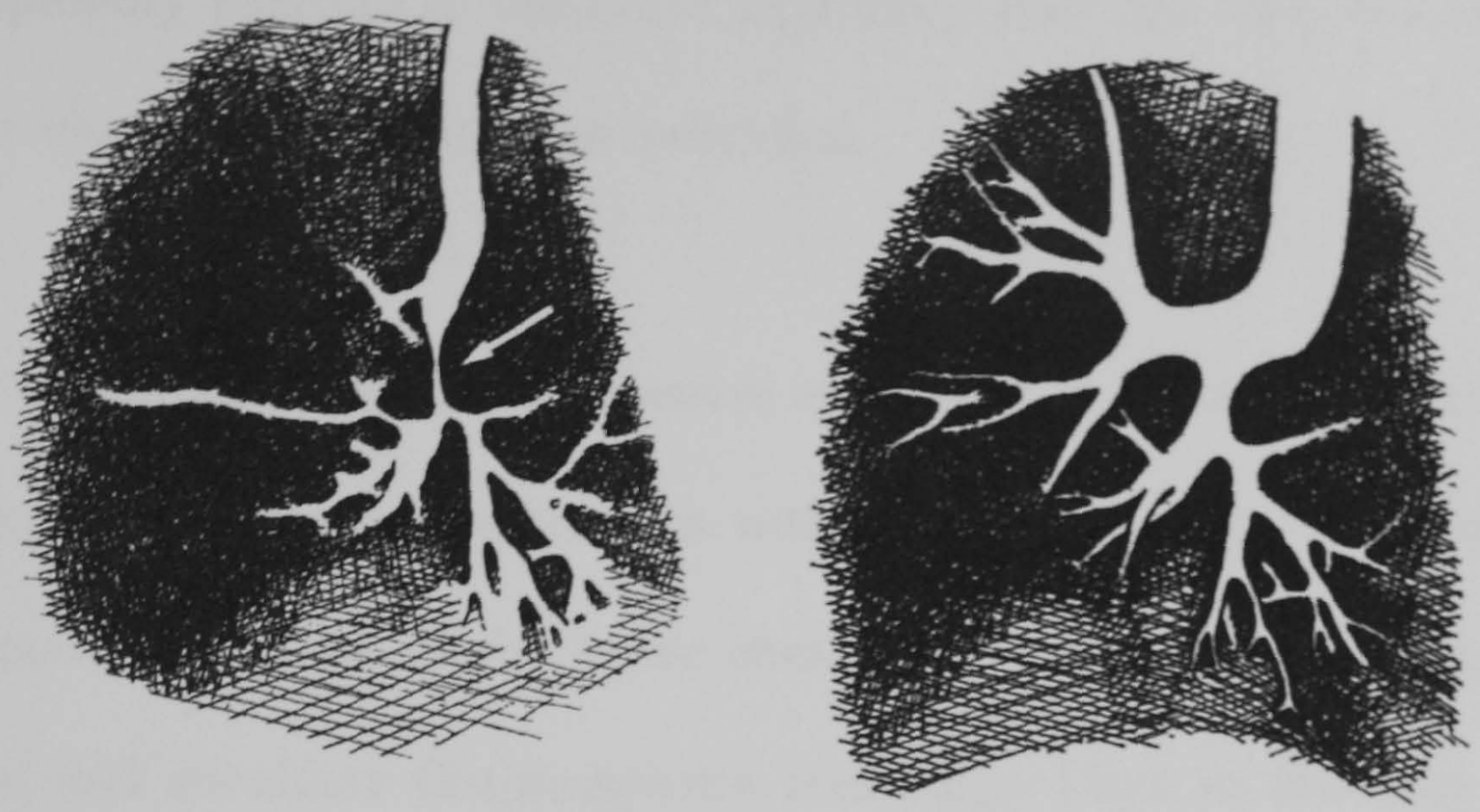
Figure 3.2: Diagrammatic representation of a forced expiratory manoeuvre showing the equal pressure point (EPP). From: Pryor 1981 (Units are in centimetres of water).

Downstream, towards the mouth, of the equal pressure point is the choke point (Dawson & Elliott 1977; Selsby & Jones 1990) and it is from this point, up towards the mouth, that there is a squeezing effect on the airway owing to the higher pressure outside the airway. Physiologically the amount of air flowing past a choke point at any instant must be equal to that flowing in less constricted parts of the airway. This is achieved by an increase in linear velocity. In addition to the squeezing effect there is also an oscillation of the airway wall as demonstrated by Freitag, Bremme & Schroer (1989) (Figure 3.14, p.106). These mechanisms, which help to loosen and move excess bronchial secretions up the airways, are therefore effective only from the proximal side of the equal pressure points.

The position of the equal pressure points is dependent on lung volume (West 1997). During normal tidal breathing and at a high lung volume the equal pressure points are said to be at the level of the carina or larger bronchi (Mead *et al* 1967). The larger

bronchi are reinforced by cartilage which prevents collapse of the airways. A cough is usually preceded by a rapid inspiration which increases lung volume and consequently the equal pressure points are in the larger more central airways. It is possible to clear progressively deeper parts of the airways by a series of coughs, without intervening inspirations, but this is more exhausting and may be more irritating on the airways than a single, continuous huff down to the same lung volume. At lung volumes above functional residual capacity, the equal pressure points are located in lobar or segmental bronchi and in the expiratory reserve volume they move towards the alveoli into quite small bronchi (Macklem 1974). Macklem also stated that the position of the equal pressure points is independent of effort and dependent on lung volume when maximal expiratory flow has been achieved.

During a cough the vocal cords close and high intrapulmonary pressures build up until on rapid abduction of the cords any foreign bodies or excess bronchial mucus are expelled with the high velocity, turbulent airflow. With a huff the vocal cords remains open and the intrathoracic pressures generated are not as high as with coughing (Langlands 1967). The mucus is gently squeezed out. Figure 3.3 demonstrates using cine-radiography (a) the central mechanical effect of coughing and (b) the more peripheral squeezing effect of a huff.



a. b.

Figure 3.3: Cine-radiographs of: (a) A cough demonstrating narrowing and collapse of the larger airways. (b) A huff demonstrating the narrowing of the smaller more peripheral airways enabling mucus to be squeezed up into the larger more central airways. From: Thompson 1963.

The increase in air flow produced by the forced expiratory manoeuvre of either a huff or a cough has a shearing effect on the airway mucus and may reduce its viscosity, in the short term (Selsby & Jones 1990), but sufficient to facilitate movement of the mucus along the airway in the direction of airflow.

Damage to the bronchial wall, owing to infection and inflammation, will inevitably cause a decrease in bronchial muscle tone and airway instability in people with cystic fibrosis. Over compliant large airways will dilate more than normal during inspiration and will exhibit a greater degree of collapse during expiration. If there is increased compression of the more central airways during huffing or coughing, this will limit the upstream movement of the equal pressure points and decrease peripheral expiratory airflow (Macklem 1974). The huff needs to be adapted to optimise airflow and to minimise collapse of the airways (Dodd 1991). For each individual there will be an

optimal expiratory pressure to maximise expiratory flow and this will vary not only among individuals, but also within an individual.

The use of the forced expiratory manoeuvre of the huff in airway clearance has, by the proponents, always been in combination with breathing control – a period of normal breathing encouraging use of the lower chest and diaphragm with relaxation of the upper chest and shoulders (diaphragmatic breathing). Used in this way there is no evidence of any increase in airflow obstruction in clinical practice (Hofmeyr, Webber, & Hodson 1986; Pryor *et al* 1979; Pryor *et al* 1994; Pryor & Webber 1979; Thompson & Thompson 1968; Webber *et al* 1986).

In vitro studies have indicated that cough is more effective in less viscous material (King 1987; King, Brock, & Lundell 1985), but Hasani *et al* (1994a) *in vivo* did not find a correlation between mucus clearance by cough or the forced expiration technique and the viscoelasticity of the sputum expectorated. These studies highlight differences between *in vitro* and *in vivo* experiments.

Ventilation

Thoracic expansion exercises and positive expiratory pressure are based on the theory of collateral ventilation via the inter-alveolar pores of Kohn, bronchiolar-alveolar channels of Lambert and inter-bronchiolar canals of Martin (Menkes & Traystman 1977) (Figure 3.4).

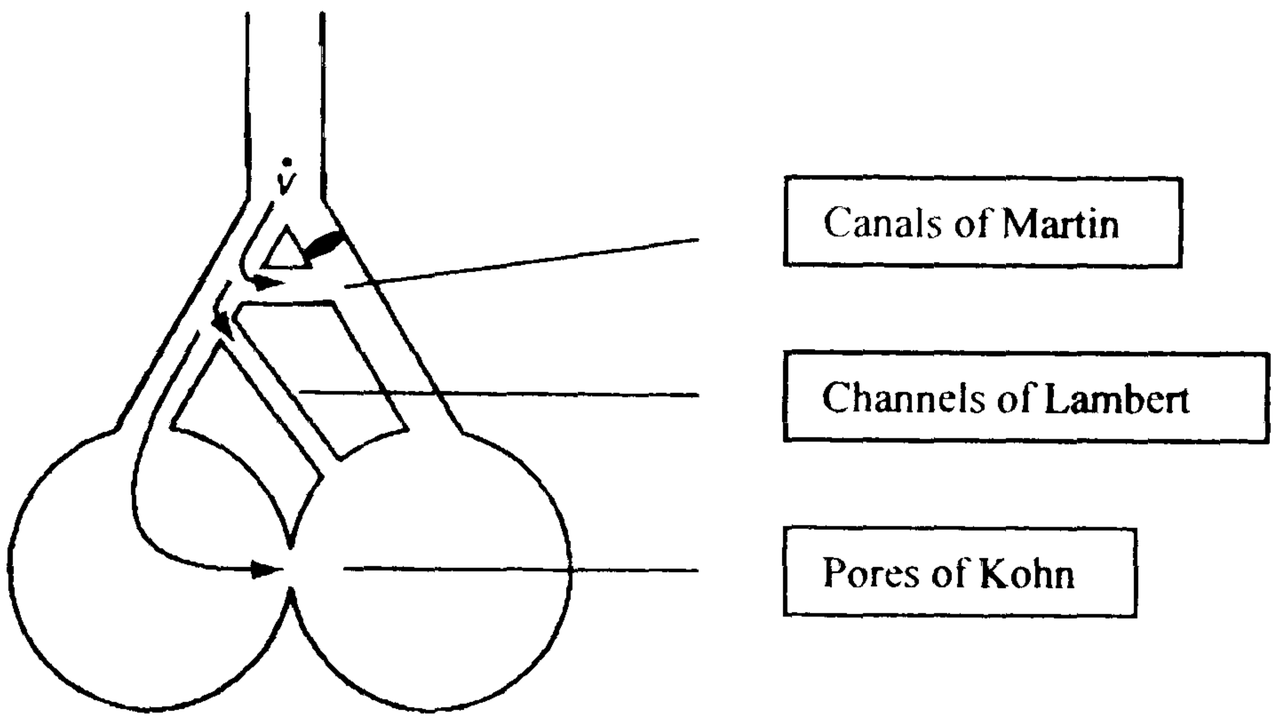


Figure 3.4: Collateral ventilation demonstrating airflow ($\dot{V}$) through the collateral channels.

There is debate as to whether the collateral ventilatory channels exist, but there is evidence in the medical literature (Macklem 1971; Menkes & Traystman 1977; Terry *et al* 1978). In post-mortem human lungs Andersen and Jespersen (1980) were able to demonstrate the existence of collateral channels in all lobes in normal lungs; and using scanning electron micrography the existence of the pores of Kohn has been demonstrated (Weibel 1984) (Figure 3.5.).

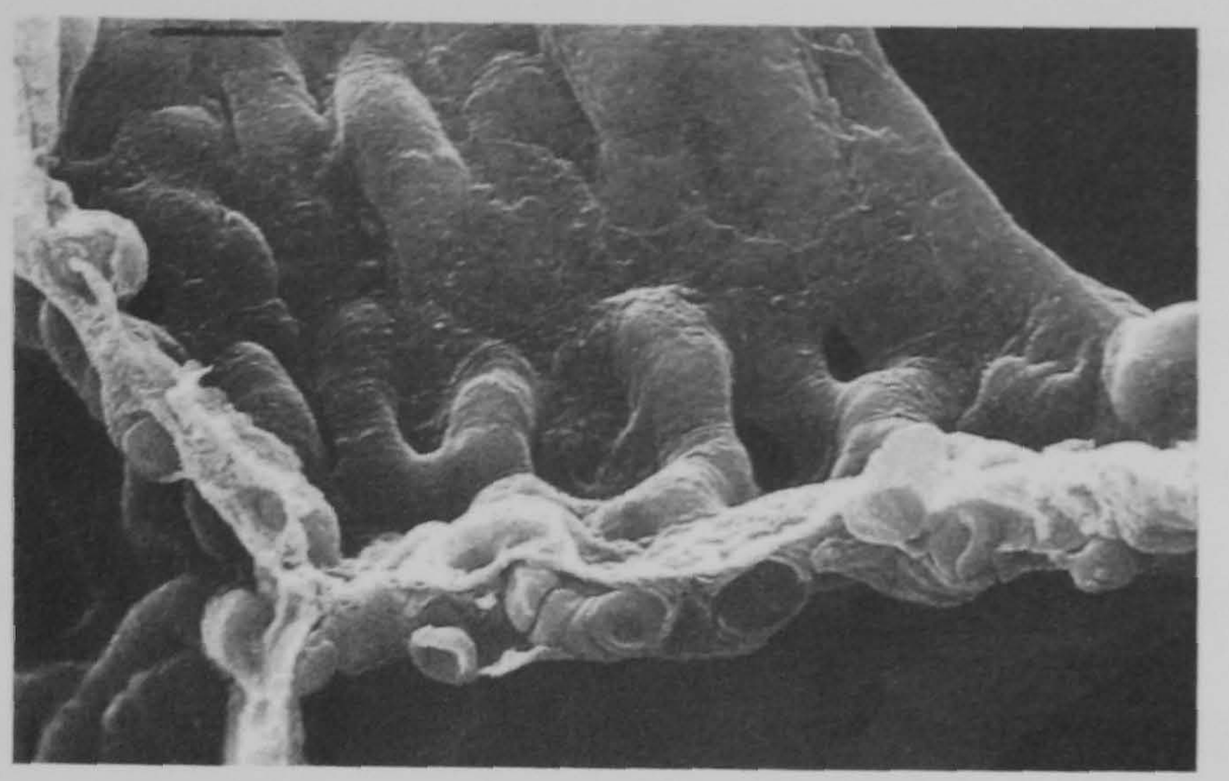


Figure 3.5. Scanning electron micrograph of the junction of three alveolar septa. Two pores of Kohn can be seen to the right of the picture. From: Weibel 1984.

In the absence of respiratory disease and when breathing at normal tidal volume, air probably does not flow via the collateral system. The resistance to airflow in these narrow channels is high and ventilation via collateral channels would take a long time in relation to the time taken for inspiration.

In the presence of lung disease, at high lung volumes and when breathing out against a positive expiratory pressure it is physically possible that these channels would enlarge, the resistance to airflow would fall and air could flow along collateral channels, building up behind secretions to then assist in loosening and mobilising them. More slowly ventilating lung units may receive part of their inspired volume from the more rapidly ventilating units via the collateral channels. This is known as Pendelluft flow. From *in vitro* work, a lower respiratory frequency and larger tidal volume should increase collateral ventilation (Elad, Shochat, & Shiner 1998).

Falk and Andersen (1991) demonstrated collateral flow in further experiments in post-mortem human lungs (Figure 3.6). In this experiment a three millimetre airway was completely blocked and the pressures across the obstruction monitored during normal

breathing and during breathing with ten centimetres of water positive expiratory pressure. In both normal lungs and lungs affected by disease. acute respiratory failure and chronic airflow limitation, the obstruction pressure swings around zero during normal breathing. When positive expiratory pressure is applied at the airway opening the obstruction pressure initially becomes negative. This would tend to move the obstruction towards the periphery, but is rapidly followed by a positive obstruction pressure tending to move the obstruction centrally. From the work by Falk and Andersen (1991), the duration of the positive obstruction period was far greater than the negative obstruction period which would culminate in movement towards the more central airways.

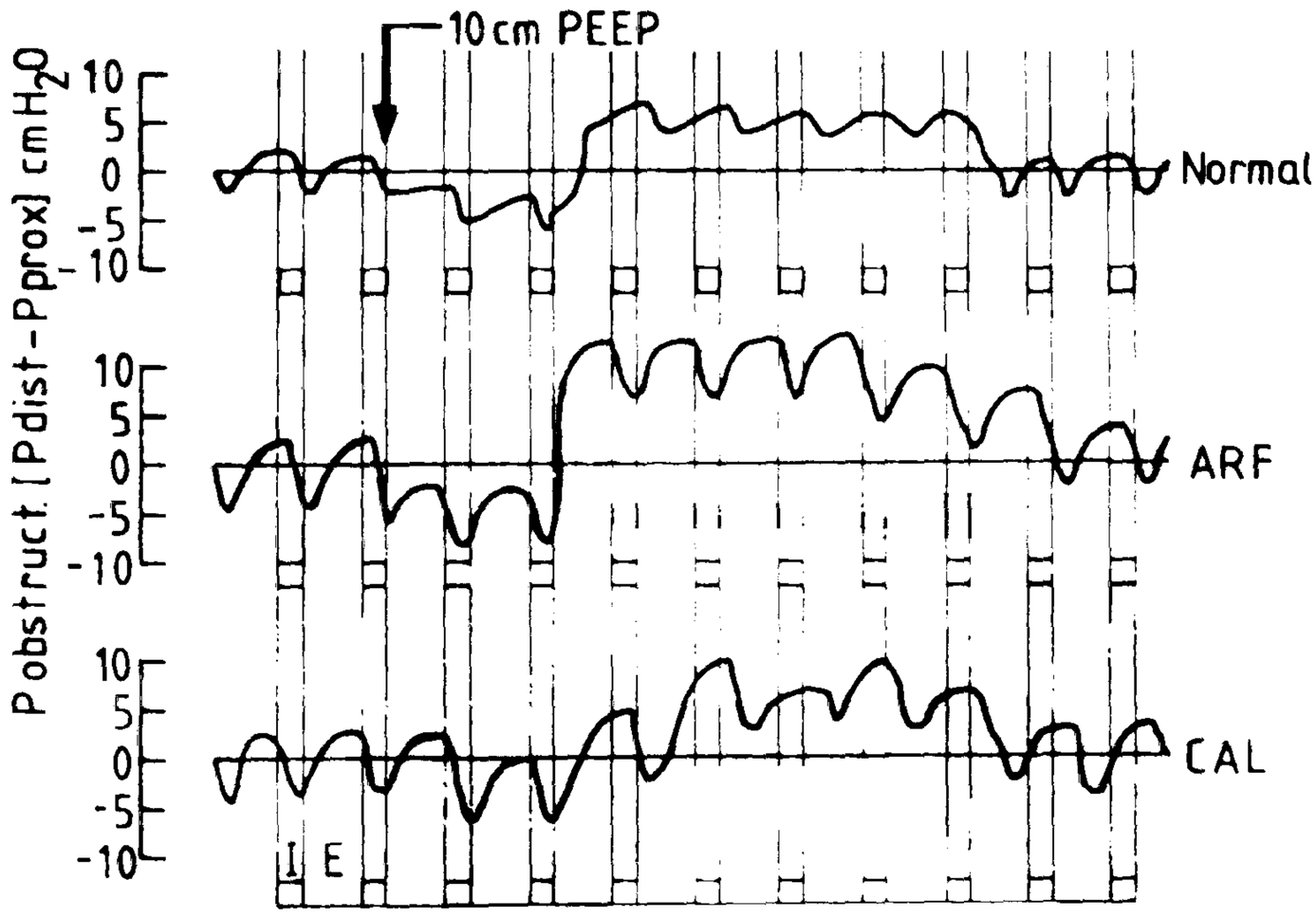


Figure 3.6: The obstruction pressure (Pobstruct on the vertical axis) is positive when the pressure distal to the obstruction exceeds the pressure proximal to the obstruction. ARF: acute respiratory failure, CAL: chronic airflow limitation. From: Falk & Andersen 1991.

With the thoracic expansion exercises and the higher resting level of breathing obtained while using positive expiratory pressure, there is also the phenomenon of interdependence (Mead, Takishima, & Leith 1970). This is the traction effect expanding alveoli exert on less well expanded alveoli which they surround (Figure 3.7). It occurs owing to the elasticity of the surrounding interstitium (Mead, Takishima, & Leith 1970) and can also take place between the lung and chest wall (Macklem 1973).

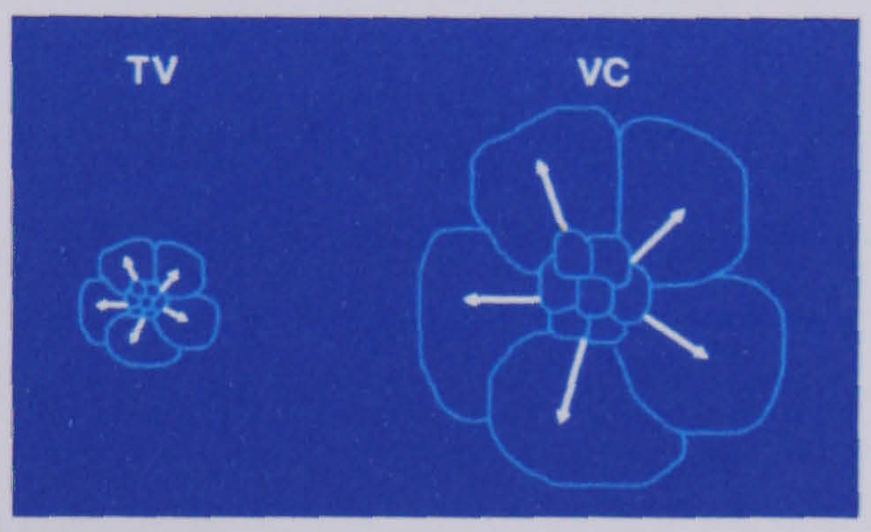


Figure 3.7: Interdependence. The effect of expanding alveoli at tidal volume (TV) and vital capacity (VC).

When breathing around tidal volume this effect is less marked than when breathing to vital capacity as with thoracic expansion exercises.

It has for many years been thought that localised thoracic expansion exercises could not influence ventilation to specific areas of the lungs, but Tucker *et al* (1999) demonstrated an initial increase in ventilation to the right lower lobe with a right unilateral lower thoracic expansion breath.

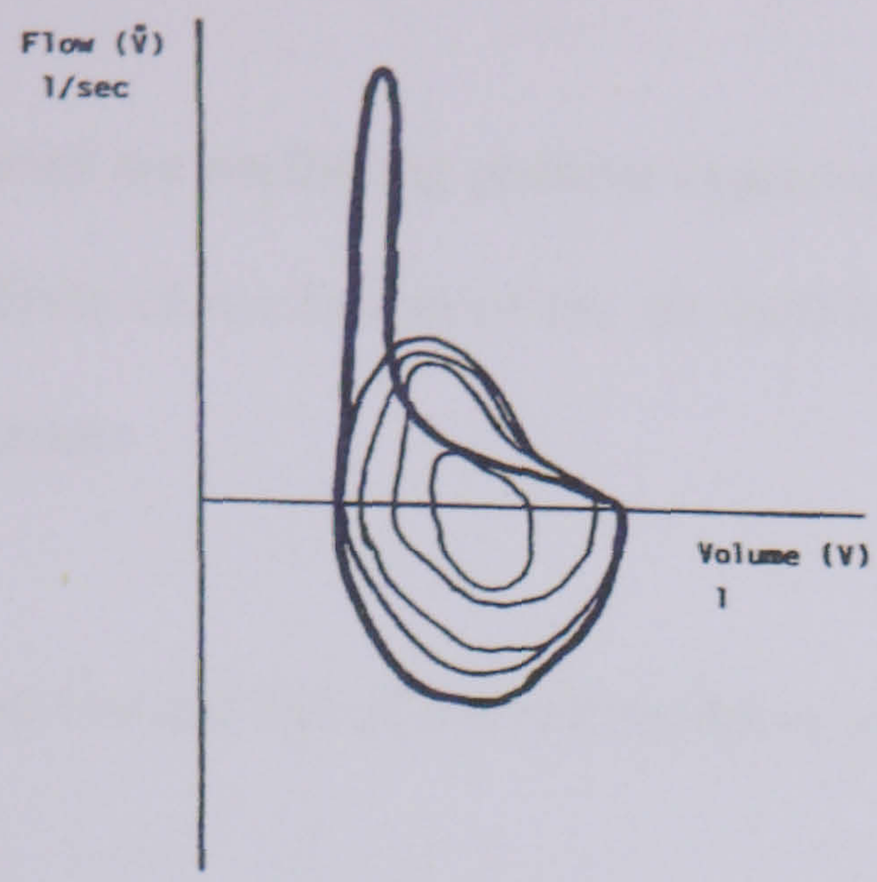
Work by Ward *et al* (1966) demonstrated that a breath which was held was more effective in reducing atelectasis than one which was not held. They concluded by

recommending a three-second pause at the end of a full inspiration to compensate for asynchronous ventilation.

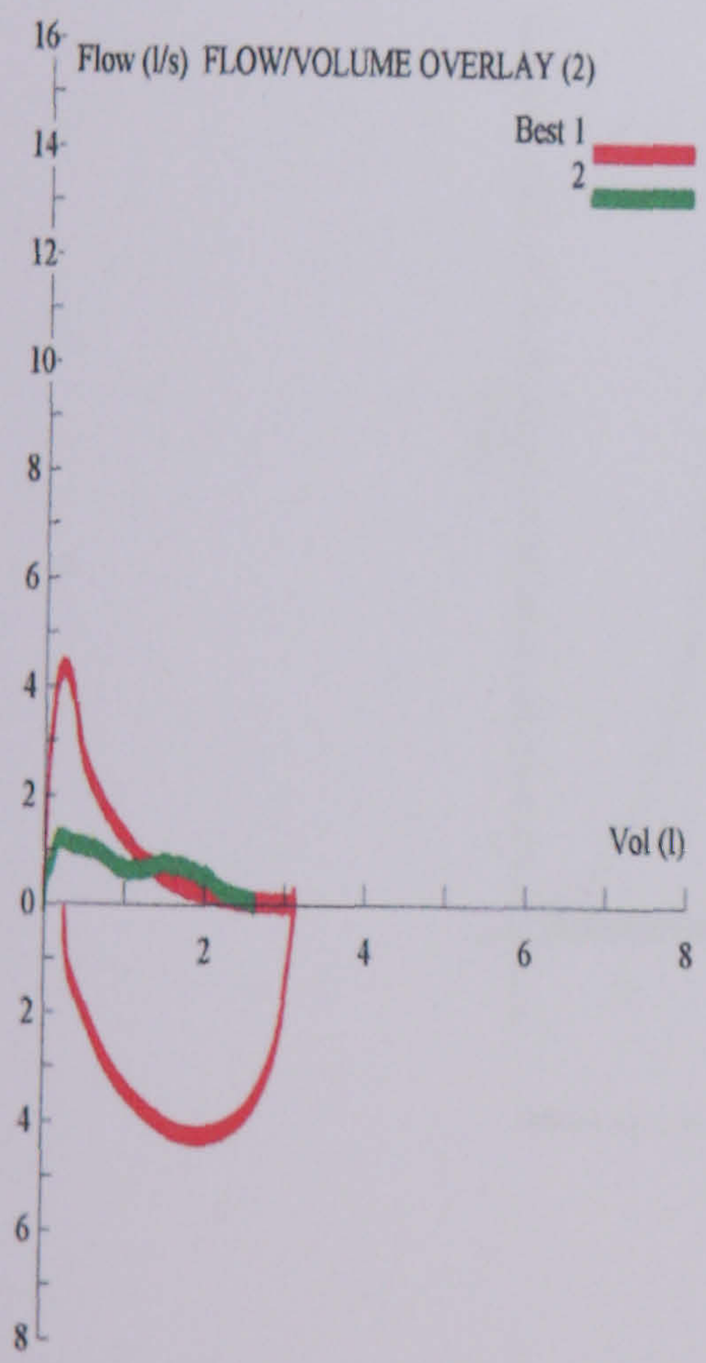
More recently Chevaillier (2000) argued that the breath hold should be with an open glottis. Chevaillier's hypothesis is that a closed glottis forms a closed system and as the air flows to less well ventilated parts of the lung it comes from better ventilated areas, which would consequently become less well ventilated. By keeping the glottis open, during the breath hold, additional air will theoretically flow into the lungs owing to the physiological principle of air moving from regions of high pressure to regions of low pressure. The pressure within the lungs will drop as air flows into the less well ventilated parts. In clinical practice this would appear to be confirmed and further work should be undertaken in this area.

Autogenic drainage is based on the principle of maximising air flow in the different generations of bronchi by controlled breathing without using any forced expiratory manoeuvre. This minimises compression of the airways. An autogenic breath can be demonstrated using the flow volume loop (Figure 3.8a and 3.8b).

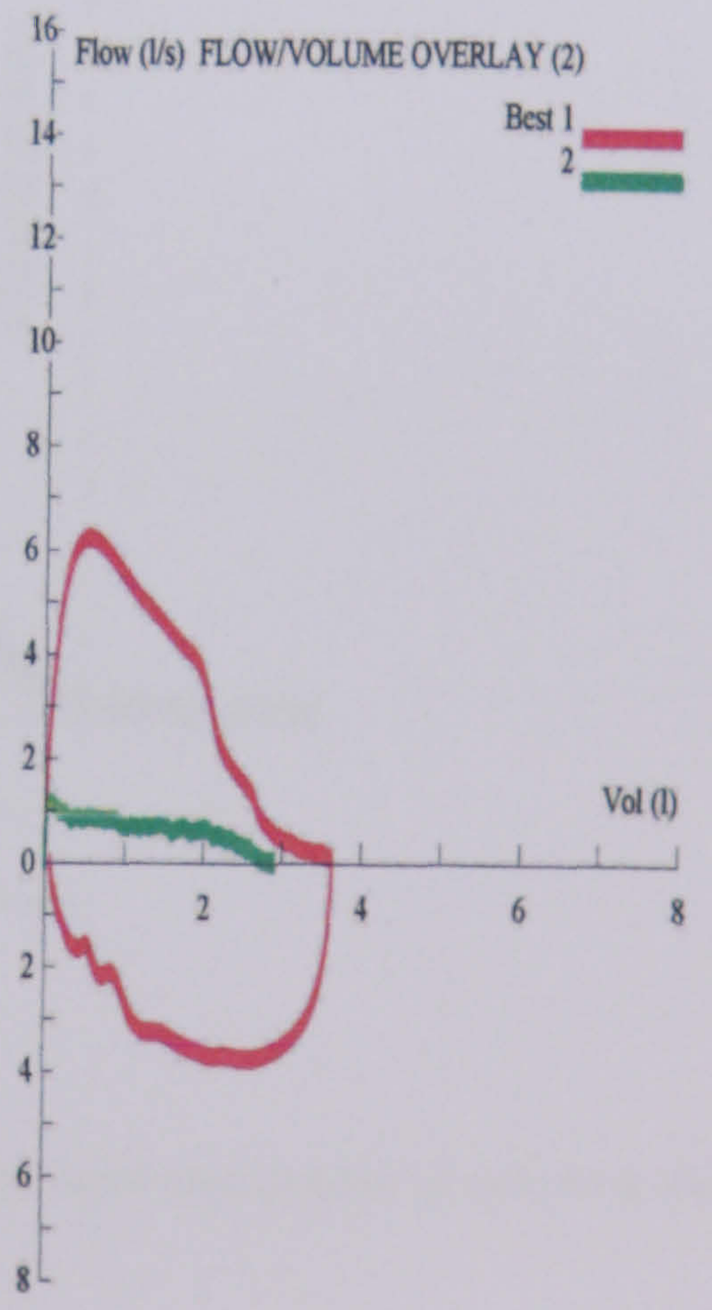
It should be noted, that the individual in Figure 3.8b has pressure dependent collapse of the airways. It is not physiologically possible to go outside the expiratory arm of the flow volume loop in the absence of lung disease (Figure 3.8c) and therefore not possible to increase expiratory flow with an unforced expiratory manoeuvre. However most people needing to use an airway clearance regimen will have lung disease, either acute or chronic, and it is likely that they will exhibit some degree of pressure dependent collapse.



a.



b.



c.

Figure 3.8: a. Diagrammatic representation of the increase in airflow, on a flow volume loop, with an unforced expiratory manoeuvre. b. Flow volume loop of one of the study subjects with cystic fibrosis. c. Flow volume loop of a subject with 'normal' lungs. The red line is a forced expiratory manoeuvre and the green line an unforced manoeuvre.

Oscillation

The flutter and cornet are oscillating positive expiratory pressure devices which utilise the mechanical effects of oscillation of the air within the airways and fluctuations in intrabronchial pressure.

With the flutter, the rise and fall of the ball produces an acceleration of airflow (Figure 3.9).

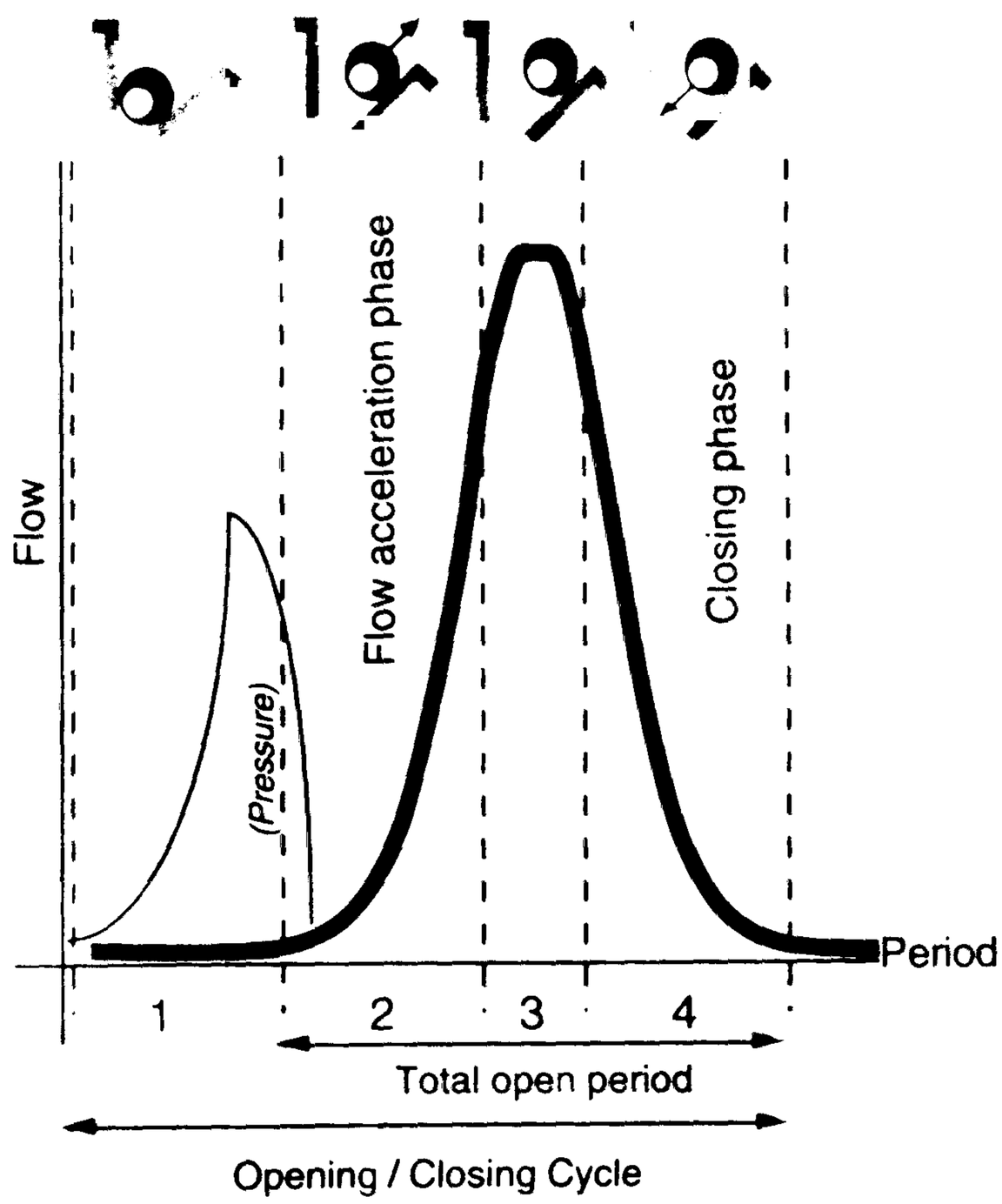


Figure 3.9: The opening and closing cycle of the flutter showing the rapid acceleration in airflow as the hole in the base of the cone opens. From: Scandipharm 1996.

With the cornet, the opening and closing of the inner tube produces an acceleration of airflow (Figure 3.10).

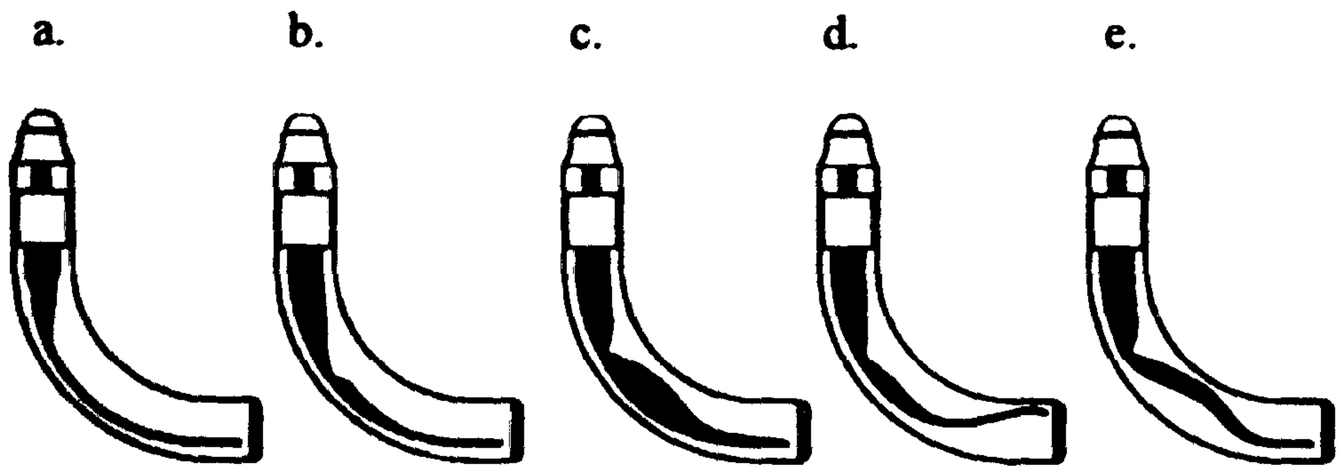


Figure 3.10: a. and b. demonstrate the buckling of the flexible inner tube, of the cornet, as the pressure increases. Figures c. and d. show the inner tube opening when the peak pressure is reached and the tube is 'catapulted' against the wall of the outer tube, releasing its pressure. Figure e. shows the process starting again resulting in an oscillatory effect. From: R.Cegla GmbH. Montabaur, Germany.

The flutter and the cornet result in different air movements. The flutter has a low frequency oscillation of between 2 and 32 Hz (Scandipharm 1996). The cornet has both low (18-25 Hz) and high frequency oscillations, with a superimposed high frequency component of about 160 Hz (Cegla 2004). Figure 3.11 and Table 3.1 (p.104) demonstrate the changes in pressure and flow for the flutter.

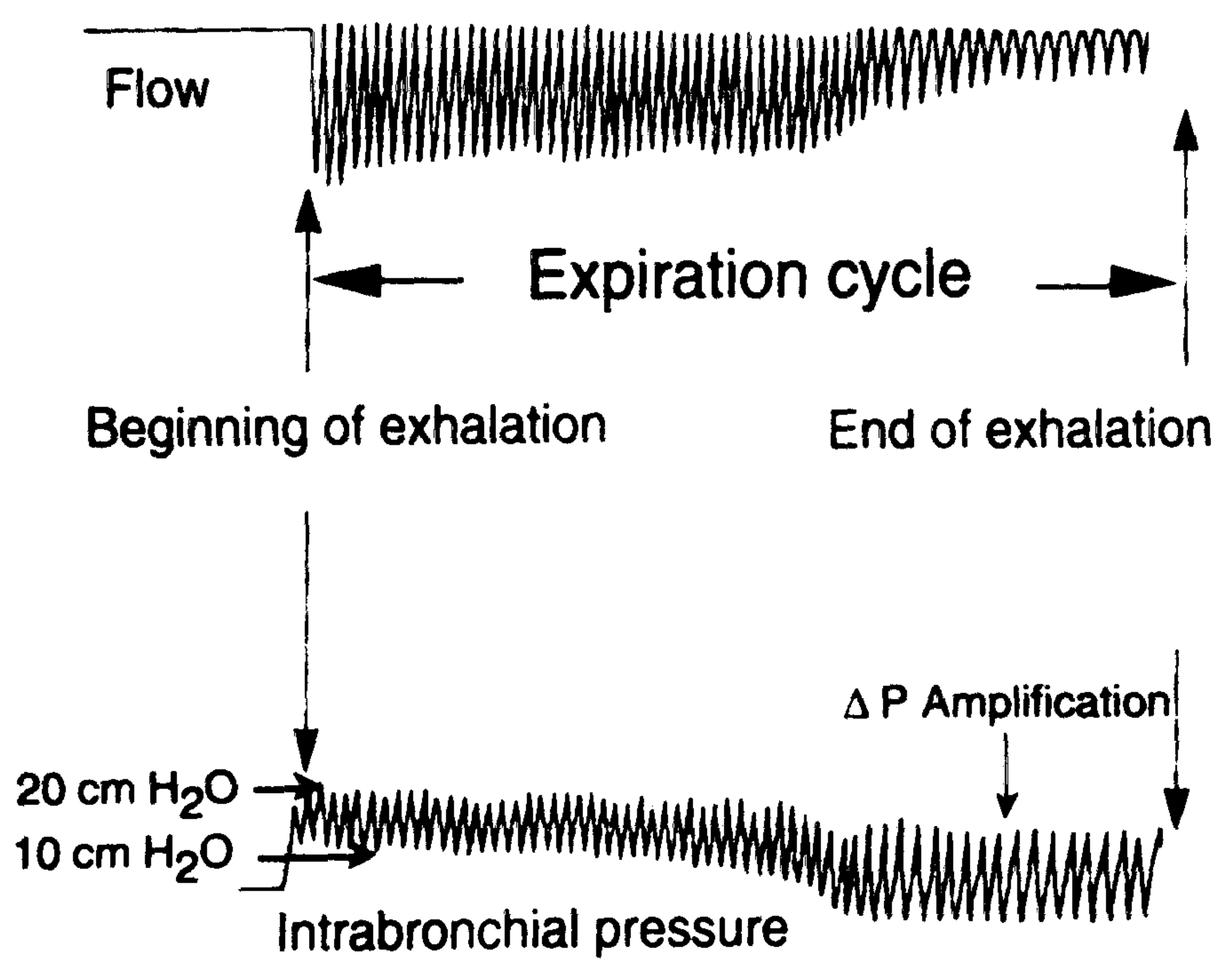


Figure 3.11: Pressure and flow characteristics of the flutter. Each oscillation represents one opening and closing cycle. A peak of intrabronchial pressure corresponds to a low in the flow curve. As the ball of the flutter rolls up, the pressure drops and the flow increases. From: Scandipharm 1996.

The flow acceleration exhibited by both the cornet and the flutter will have a shearing effect on the mucus, reducing its viscosity in the short-term. to facilitate the movement of mucus up the airways. Figures 3.12a and 3.12b demonstrate the changes in pressure and flow for the cornet.

The mouthpiece of the cornet can be rotated from the 'initial' position through positions '2', '3' and '4'. This action twists the mouthpiece end of the flexible inner tube with a consequent increase in positive expiratory pressure and reduction in the frequency of the oscillations (Table 3.1, p.104).

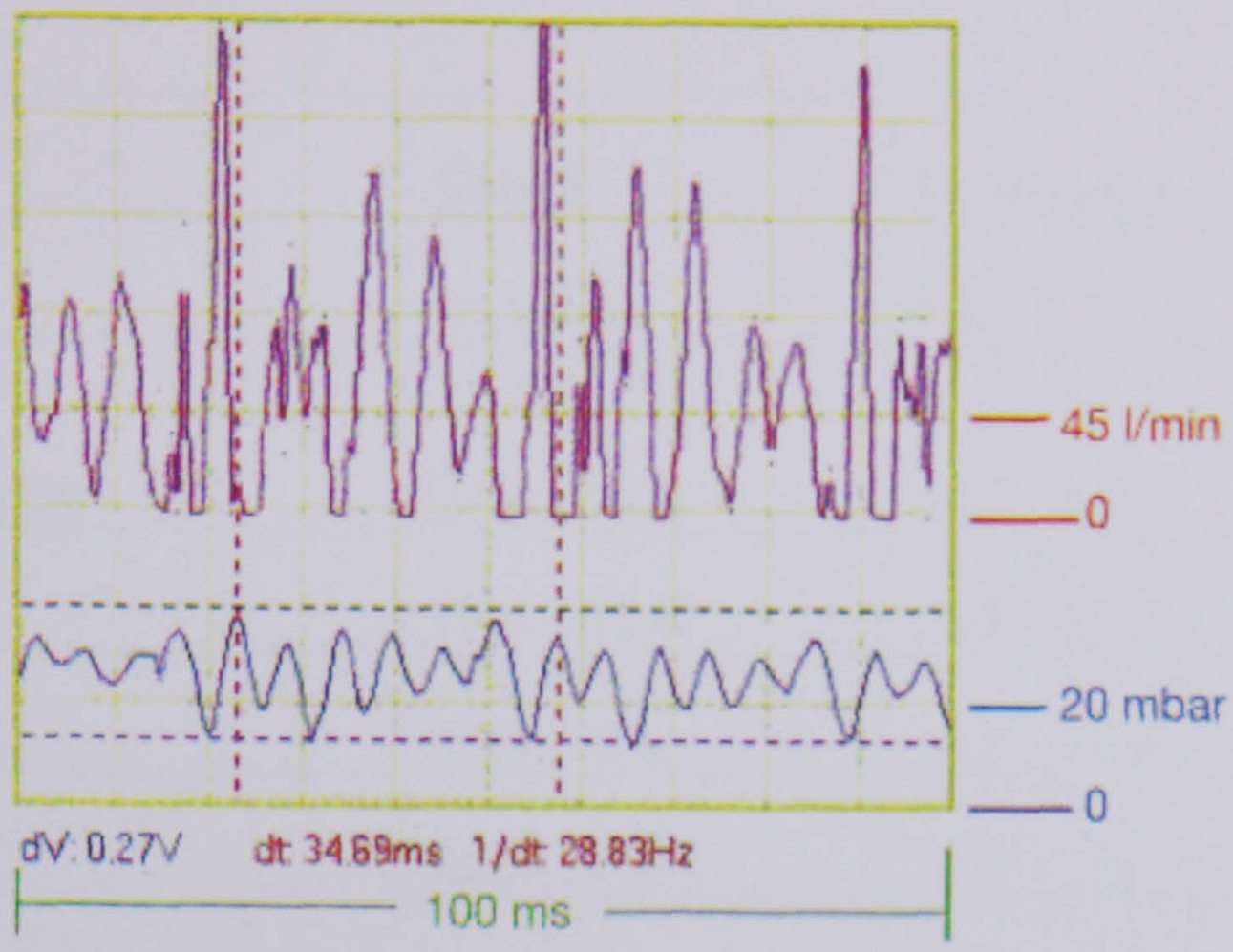
By twisting the mouthpiece, the cornet can be changed from 'continuous' PEP (Initial position to Position 2) to 'dynamic' PEP (Position 3 to Position 4) (Cegla 2004). The pressure amplitude of the cornet in Position 3 to Position 4 resembles the flutter, but the shapes of the pressure curves are different; the flutter increases in a sinusoidal way (Figure 3.11), whereas the cornet increases in a trapezoid form (Figure 3.12b).

The amplitude of the flow changes are less with the flutter than with all positions of the cornet. As the ball in the flutter lifts, expiratory air escapes freely from the system without inducing any oscillations ('bypass' air) (Figure 3.9, p.100). With the cornet, all the expiratory air passes through the tube and is transformed to pressure and flow variations. This may explain how the cornet can be used in patients with a very low forced expiratory volume in one second.

'Continuous' PEP may assist mucociliary clearance by its effect of increasing collateral flow (Falk & Andersen 1991). 'Dynamic' PEP may assist mucociliary clearance by its effect on the viscoelasticity of mucus (App *et al* 1998) and consequent facilitation of the

movement of mucus in a cephalad direction (Cegla 2004).

a) Position 2 - slight twist of the flexible inner tube from the mouthpiece end.



b) Position 4 - further twist of the flexible inner tube from the mouthpiece end.

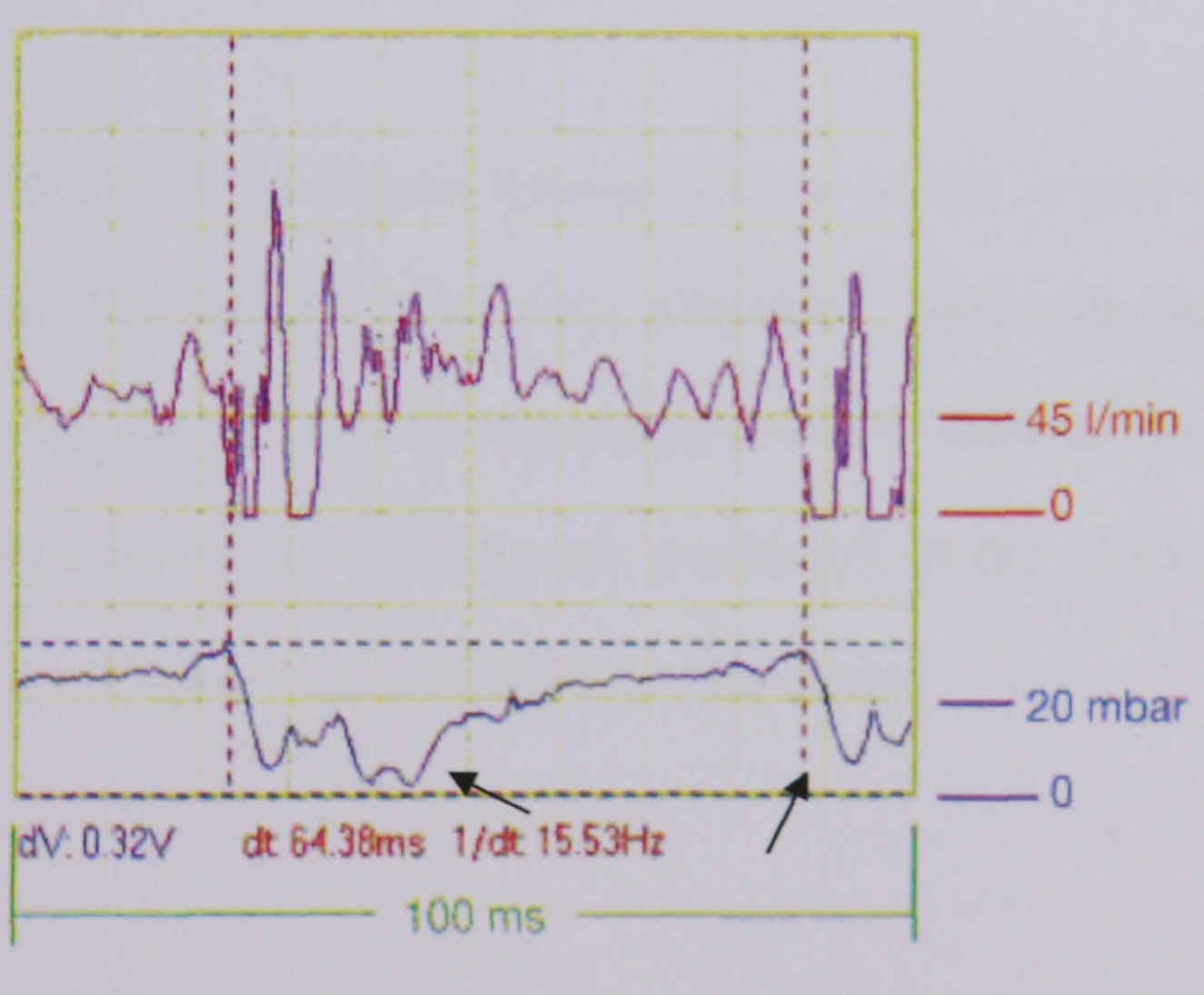


Figure 3.12: Pressure and flow characteristics of the cornet (Courtesy of Professor U. Cegla). Flow (purple upper traces) is in litres per minute and pressure (blue lower traces) is in millibars.

(a.) Demonstrates the flow and pressure with the cornet in position 2. This is 'continuous' PEP.

(b.) Demonstrates the flow and pressure with the cornet in position 4. This is 'dynamic' PEP where the pressure builds up and then drops as seen in the lower pressure trace indicated by the arrows.

Pressures (cm H_2O) generated by the flutter and cornet		
	Mouth	**Peripheral**
Flutter	20.5 – 4.9	9.6 – 3.7
Cornet Initial Position:	24.3 – 14.5	14.4 – 14.1
Position 2:	27.4 – 10.9	16.5 – 13.4
Position 3:	31.5 – 3.4	15.7 – 10.8
Position 4:	25.3 – 1.1	17.6 – 7.5

Table 3.1: The mouth and intrabronchial pressures of the flutter and cornet (Cegla 2004).

Video film, undertaken at the Cystic Fibrosis Center of the Rainbow Babies and Children's hospital, Case Reserve University, Cleveland, Ohio with participation by Doctors MW Konstan, RC Stern and CF Doershuk is said to illustrate the effects of the vibration of the bronchial walls and upwards movement of the mucus from the 5^{th} generation of airways (Figure 3.13) with the use of the flutter.

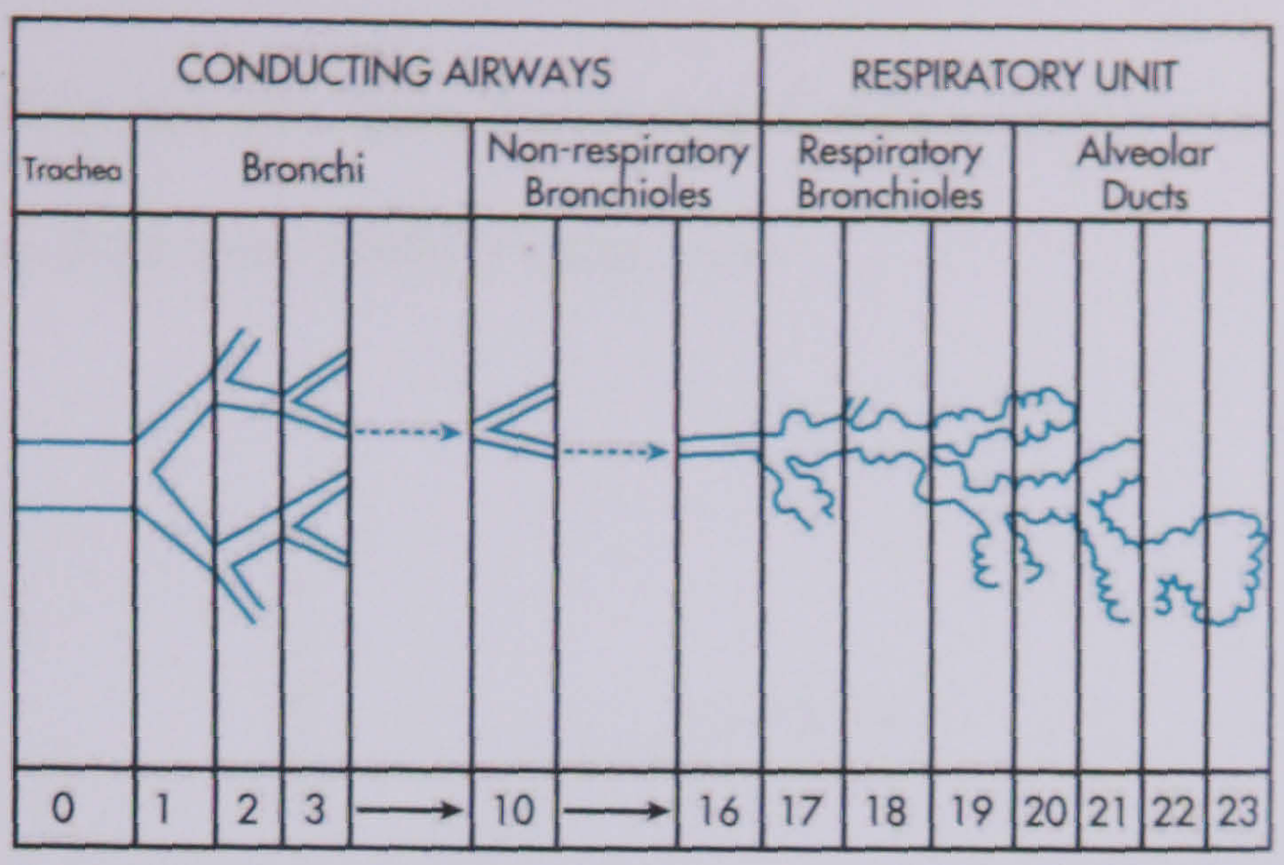


Figure 3.13: The generations of the airways. The numbers at the bottom indicate the approximate number of generations from the trachea to the alveoli. In the human, this may vary from as few as 10 to as many as 27. From: Weibel 1963.

The diameter of the bronchi decrease with each generation of airway (Weibel 1963):

0 = trachea

1 – 4 = carina to lobar bronchi

5 – 16 = lobar bronchi to terminal bronchi

17 – 19 = respiratory bronchioles

20 – 23 = alveoli (Weibel 1963).

Hasani *et al* (1994b) have said that it is reasonable to suggest that both the cough and the huff of the forced expiration technique are probably at least effective down to airways equivalent to generations 10 or 12. Others have postulated that cough may be effective in clearing secretions from the trachea down to the 7th or 8th generation (Leith 1968).

An oscillatory effect has also been demonstrated with a forced expiratory manoeuvre (Freitag, Bremme, & Schroer 1989) (Figure 3.14).

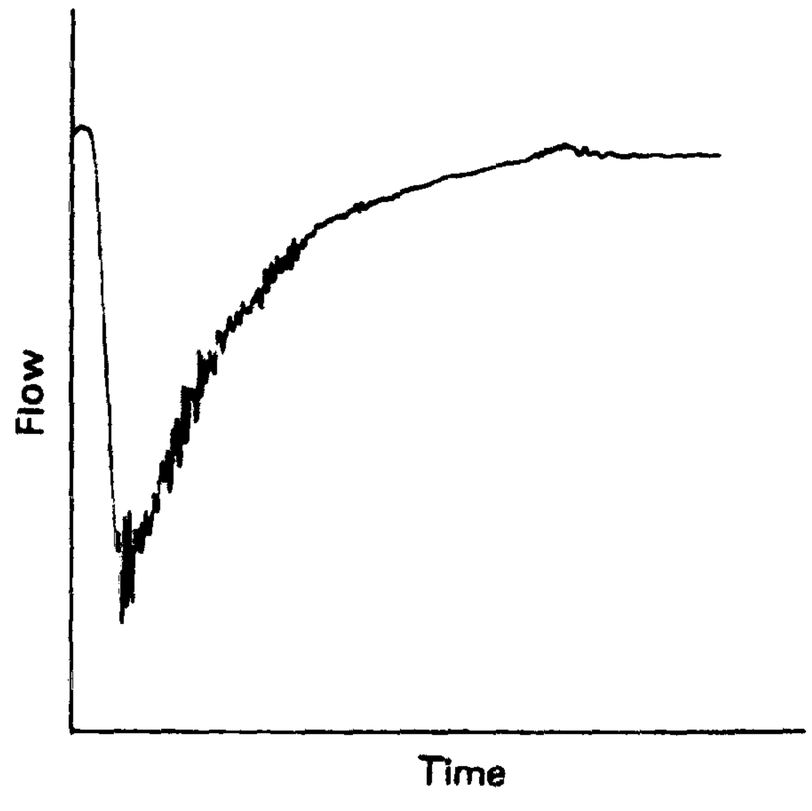


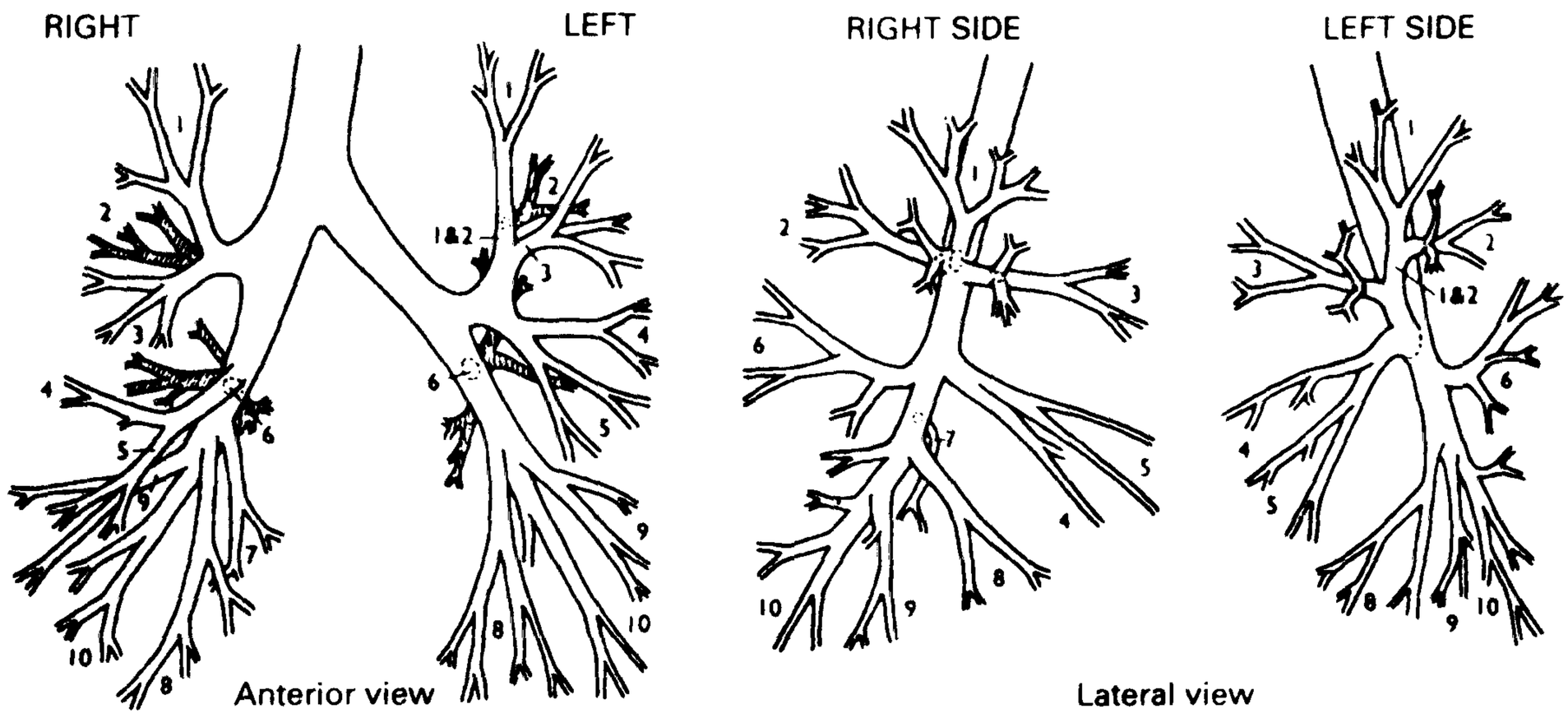
Figure 3.14: A flow curve during a force expiratory manoeuvre showing the 'intrinsic vibrations'. From: Freitag, Bremme, & Schroer 1989.

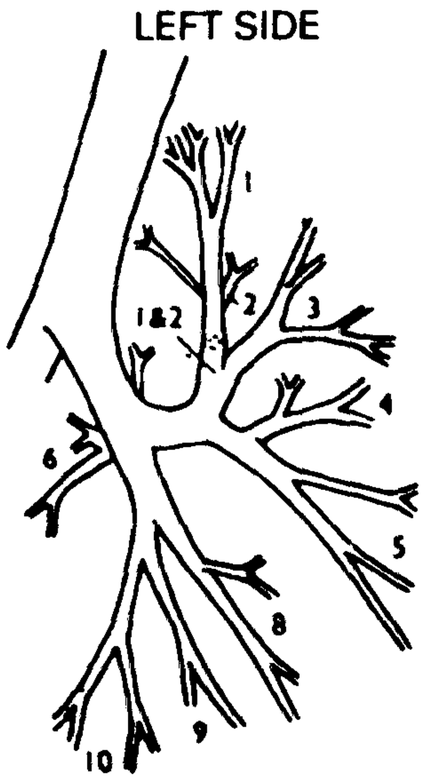
Gravity

Gravity assisted positioning can be used to:

- assist the clearance of bronchial secretions
- improve ventilation and perfusion (Pryor *et al* 2002).

Nelson (1934) described the use of positioning to assist the drainage of secretions from the lungs based on the anatomy of the bronchial tree (Figure 3.15).





	Right lung	Left lung	
Upper lobe	1. Apical	1. Apical	
	2. Posterior	2. Posterior	
	3. Anterior	3. Anterior	
Middle lobe	4. Lateral	4. Superior	Lingula
	5. Medial	5. Inferior	Lingula
Lower lobe	6. Apical	6. Apical	
	7. Medial basal (cardiac)	7. —	
	8. Anterior basal	8. Anterior basal	
	9. Lateral basal	9. Lateral basal	
	10. Posterior basal	10. Posterior basal	

Figure 3.15: Bronchopulmonary nomenclature approved by the Thoracic Society (1950). From: Pryor *et al* 2002.

The positions associated with this nomenclature are described in Table 3.2.

Lobe		Position	
Upper lobe	**1** Apical bronchus	**1**	Sitting upright
	2 Posterior bronchus (a) Right	**2a**	Lying on the left side horizontally turned 45° on to the face, resting against a pillow, with another supporting the head
	(b) Left	**2b**	Lying on the right side turned 45° on to the face, with three pillows arranged to lift the shoulders 30 cm (12 in) from the horizontal
	3 Anterior bronchus	**3**	Lying supine with the knees flexed
Lingula	**4** Superior bronchus **5** Inferior bronchus	**4 & 5**	Lying supine with the body a quarter turned to the right maintained by a pillow under the left side from shoulder to hip. The chest is tilted downwards to an angle of 15°
Middle lobe	**4** Lateral bronchus **5** Medial bronchus	**4 & 5**	Lying supine with the body a quarter turned to the left maintained by a pillow under the right side from shoulder to hip. The chest is tilted downwards to an angle of 15°
Lower lobe	**6** Apical bronchus	**6**	Lying prone with a pillow under the abdomen
	7 Medial basal (cardiac) bronchus	**7**	Lying on the right side with the chest tilted downwards to an angle of 20°
	8 Anterior basal bronchus	**8**	Lying supine with the knees flexed and the chest tilted downwards to an angle of 20°
	9 Lateral basal bronchus	**9**	Lying on the opposite side with the chest tilted downwards to an angle of 20°
	10 Posterior basal bronchus	**10**	Lying prone with a pillow under the hips and the chest tilted downwards to an angle of 20°

Table 3.2: Gravity assisted positions. From: Pryor *et al* 2002.

Figure 3.16 shows the position which was, for many years, adopted for drainage of the lower lobes (posterior basal segments).



Figure 3.16: Positioning for posterior basal segments of the lower lobes in the 1940's.

The beneficial effects of gravity, in people with cystic fibrosis, had been demonstrated by Wong *et al* (1977) using radionuclide imaging techniques. They identified that an abnormal tracheal mucus clearance approached normal when the subjects were placed

in a 25 degree head-down tipped position.

The use of gravity assisted positioning, as a part of the regimen of the active cycle of breathing techniques, had continued and this was supported by the results of the study by Hofmeyr, Webber and Hodson (1986). In addition Steven *et al* (1992) had compared cough in the sitting position, the active cycle of breathing techniques in the sitting position and the active cycle of breathing techniques in the head-down tipped position. More sputum was cleared during a treatment session with the active cycle of breathing techniques in the head-down tipped position.

Lannefors and Wollmer (1992), using inhaled radiolabelled particles, found that during 'postural drainage' mucus clearance was greater from the dependent lung rather than the uppermost lung. This suggests that the effect of the increase in regional lung ventilation may be greater than the direct effect of gravity on mucus, in mucus clearance.

The Danes however had changed to the positive expiratory pressure regimen in the sitting position as a consequence of their study (Falk *et al* 1984). Similarly the flutter was used in the sitting position (Konstan, Stern, & Doershuk 1994) and the cornet has, from its instigation, been used in the sitting position (Cegla *et al* 1997).

The increased effectiveness in the medical management of people with cystic fibrosis – improved antibiotic regimens (including inhaled antibiotics), mucolytics (for example Dornase alfa), improved nutrition, more effective airway clearance regimens and the development of specialist centres have increased longevity and quality of life. If the study by Hofmeyr, Webber & Hodson (1986) was to be repeated today, 18 years later, it is probable that the effects of gravity would be less significant. *Pseudomonas*

aeroginosa has become the dominant organism in people with cystic fibrosis. Before this, and up to the 1980's, the dominant organism had been *Staphylococcus aureus*, with the consequent formation of *staphylococcus* abscess cavities and these drained more effectively when the cavity was positioned with its opening facing downwards.

Cecins *et al* (1999a) compared the use of the active cycle of breathing techniques with a 'head-down' tilt and without a 'head-down' tilt (side lying) in 19 subjects with bronchiectasis. Thirteen of these subjects had bronchiectasis as a consequence of cystic fibrosis and it is therefore this group, rather than those with bronchiectasis not associated with cystic fibrosis, which may have influenced their findings. All subjects were producing more than 20 grams of sputum per day. There were no significant differences in the wet weight of sputum expectorated between either of the regimens. The perception of breathlessness was significantly increased with the head-down tipped position. The authors concluded that the side lying position could be used as an alternative in these patients and may improve adherence to treatment as it is more comfortable.

With gravity assisted positioning there are changes in both ventilation and perfusion. In the adult, both ventilation and perfusion are preferentially distributed to the dependent parts of the lung (West 1997). In children it is the uppermost lung regions which are preferentially ventilated (Davies *et al* 1985). Lannefors and Wollmer (1992) have demonstrated how this phenomenon can influence the movement of bronchial secretions.

It is probable, in adults, that the increase in ventilation to the more compliant and dependent parts of the lung will assist the loosening and mobilising of excess bronchial

secretions in these regions, and distension of the uppermost parts of the lung will also assist the loosening and mobilising of excess secretions. It is likely that mucus is mobilised and cleared from both dependent and non-dependent parts of the lungs during an effective airway clearance regimen in both the side lying (Figure 3.17) and sitting (Figure 3.18) positions.



Figure 3.17: The side lying position.



Figure 3.18: The sitting position.

The inclusion of self chest clapping, to an effective airway clearance regimen, in people with cystic fibrosis, who were clinically stable, conferred no demonstrable additional benefit (Webber *et al* 1985). This finding should not however be extrapolated to the patient with an acute pulmonary exacerbation of infection.

Chapter IV. Outcome Measures

Lung function

Spirometry is said to have begun with Hutchinson in 1846 with the introduction of the slow vital capacity measurement. However this measurement was not particularly useful in diseases such as asthma when it was the decreased ability to exhale that was of interest to the clinician. Tiffeneau and Pinelli in 1947 are credited, by Milic-Emili, Koulouris & D'Angelo (1999), to have introduced the measurement of volumes exhaled in a given period of time, including the forced expiratory volume in one second during a forced vital capacity manoeuvre. Hyatt, Schilder & Fry followed with the maximal expiratory flow-volume loop in 1958.

Spirometry measures the volume of air expired or inspired as a function of time. Either quiet breathing (tidal volume) can be measured, or a deep inspiration or expiration to give information on vital capacity. Spirometry can also be used to measure flow and volume, but it cannot measure absolute lung volume. It can measure the amount of air entering and leaving the lungs, but it cannot measure the total amount of air contained within the lungs.

The forced vital capacity (FVC) is the volume of gas delivered during an expiratory manoeuvre which is made as rapidly and completely as possible starting from full inspiration (Quanjer 1983). It is to be distinguished from the relaxed or slow expiratory vital capacity, where the emphasis is on the completeness of the manoeuvre rather than the speed. The forced expiratory volume in one second (FEV_1) is the volume of gas exhaled in the first second of the forced vital capacity manoeuvre (Quanjer 1983). The

FEV_1 / FVC percentage or ratio provides a measure of airflow obstruction.

Whole body plethysmography can be used to obtain information about thoracic gas volumes. It is based on Boyle's law which states that the volume of a fixed quantity of gas at a constant temperature varies inversely with the pressure. The patient sits inside an airtight box and inhales and exhales to a particular lung volume, usually functional residual capacity, and then a shutter drops across the breathing tube. The patient makes an inspiratory effort against the closed shutter causing the chest volume to expand while decompressing the air in the lungs. The increase in chest volume slightly reduces the box volume and slightly increases the pressure in the box. Using Boyle's Law ($P_1V_1 = P_2V_2$ where P=pressure and V=volume), the original volume of air in the lungs can be calculated (functional residual capacity). The residual volume is derived by subtracting the expiratory reserve volume from the functional residual capacity.

During childhood and adolescence there is a natural rise in lung function (Tager *et al* 1988). This increase may continue into the third or even fourth decade (Kerstjens *et al* 1997), but the European Community for Coal and Steel states that there is no change between the ages of 18 to 25 years and an age of 25 years should be entered into the regression equation for this whole age range (Quanjer 1983). Using this regression equation the average yearly decline in lung function (forced expiratory volume in one second [FEV_1]) is approximately 29 millilitres for men and 25 millilitres for women, but care must be taken in using this data as the equations were derived from cross sectional data, rather than longitudinal data, and over 20 years ago (Kerstjens *et al* 1997). This represents a fall of -0.2 to -0.5% per annum or -2 to -5% per decade (Cramer 2002).

For people with cystic fibrosis the rate of deterioration of FEV_1 is currently recognised as approximately -2% per annum (Cystic Fibrosis Foundation 2004). Figure 4.1 shows that since 1990 (Cystic Fibrosis Foundation 2003), lung function (forced expiratory volume in one second, FEV_1) has improved 5 to 10 percent for all ages from 6 to 30 years in people with cystic fibrosis.

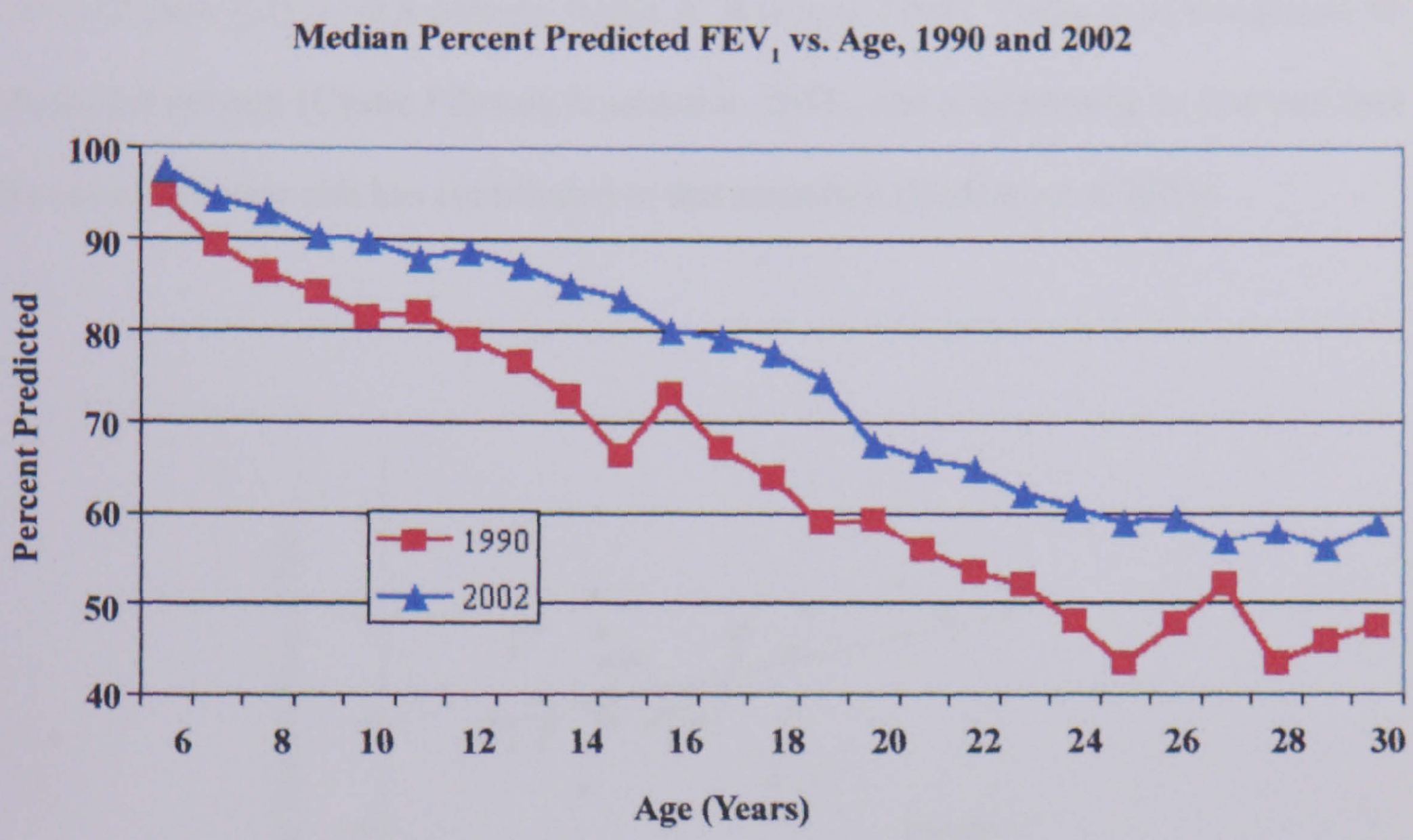


Figure 4.1: From: Cystic Fibrosis Foundation 2003.

Forced expiratory volume in one second (FEV_1) is often near normal, in children with cystic fibrosis, when first measured at about 6 years of age. A reduction in FEV_1 of less than 30% predicted has been identified as a significant predictor of mortality (Corey & Farewell 1996; Kerem *et al* 1992), but is known to be variable within a given subject and to a greater degree in people with cystic fibrosis than in normal controls (Cooper *et al* 1990; Nickerson *et al* 1980). With the marked improvements in the health of people with cystic fibrosis, FEV_1 is becoming a less sensitive indicator of morbidity today but

at the time of setting up the study it was considered a valid and sensitive primary outcome measure.

The expected rate of decline in forced expiratory volume in one second (FEV_1), as a percent of predicted FEV_1, has ranged from -2.3 percent (Davis, Byard, & Konstan 1997) with the rate of decline decreasing with increasing age (Davis, Byard, & Konstan 1997) (Figure 4.2) to -0.8 percent (Milla & Warwick 1998). Today it is recognised as about -2.0 percent (Cystic Fibrosis Foundation 2004), but is continuing to decrease and the use of Dornase alfa has contributed to this reduction (Hodson *et al* 2003).

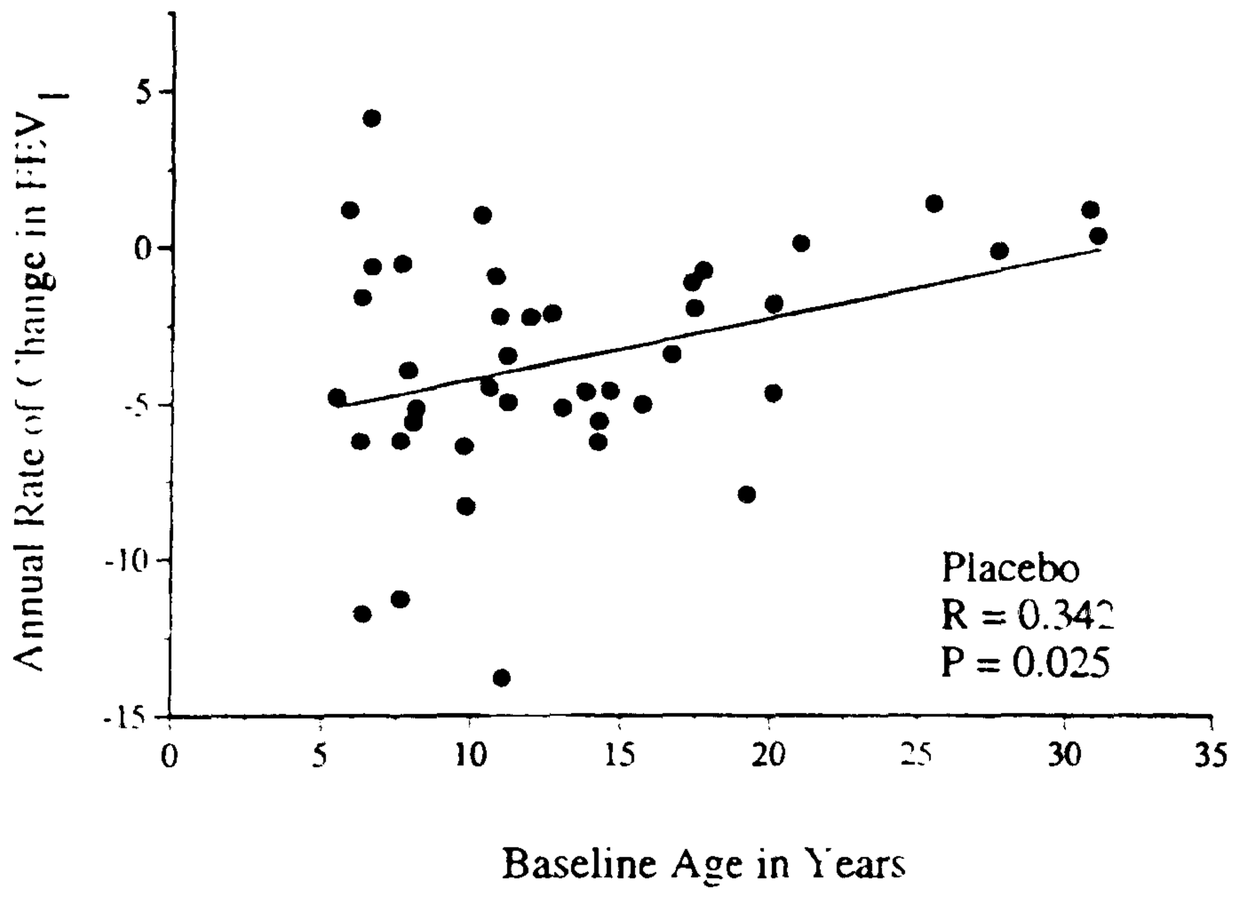


Figure 4.2: Rate of change of forced expiratory volume in one second (FEV_1) as a function of age in patients with cystic fibrosis. From: Davis, Byard, & Konstan 1997.

The lung function measurements, for this thesis, were undertaken in association with the subject's clinical annual review. The measurements identified as being of interest, in addition to the primary outcome measure of forced expiratory volume in one second (FEV_1), were:

- Forced vital capacity (FVC)
- Maximal expiratory flow at 25 percent of forced vital capacity (MEF_{25}), to reflect small airway function
- Residual volume as a percent of total lung capacity (RV%TLC), to reflect lung hyperinflation.

The tests were performed by the Lung Function Department at Royal Brompton & Harefield NHS Trust, in accordance with the Guidelines for the Measurement of Respiratory Function (British Thoracic Society and the Association of Respiratory Technicians and Physiologists 1994).

Body mass index

There appears to be a positive association between survival in people with cystic fibrosis and body weight as an indicator of nutritional status (Corey *et al* 1988; Kraemer *et al* 1978). Stead, Hodson and Batten (1987) identified significant improvements in lung function and increases in body weight during courses of nebulised antibiotics. Nir *et al* (1996) found a strong correlation between body mass index (BMI) and lung function in people with cystic fibrosis.

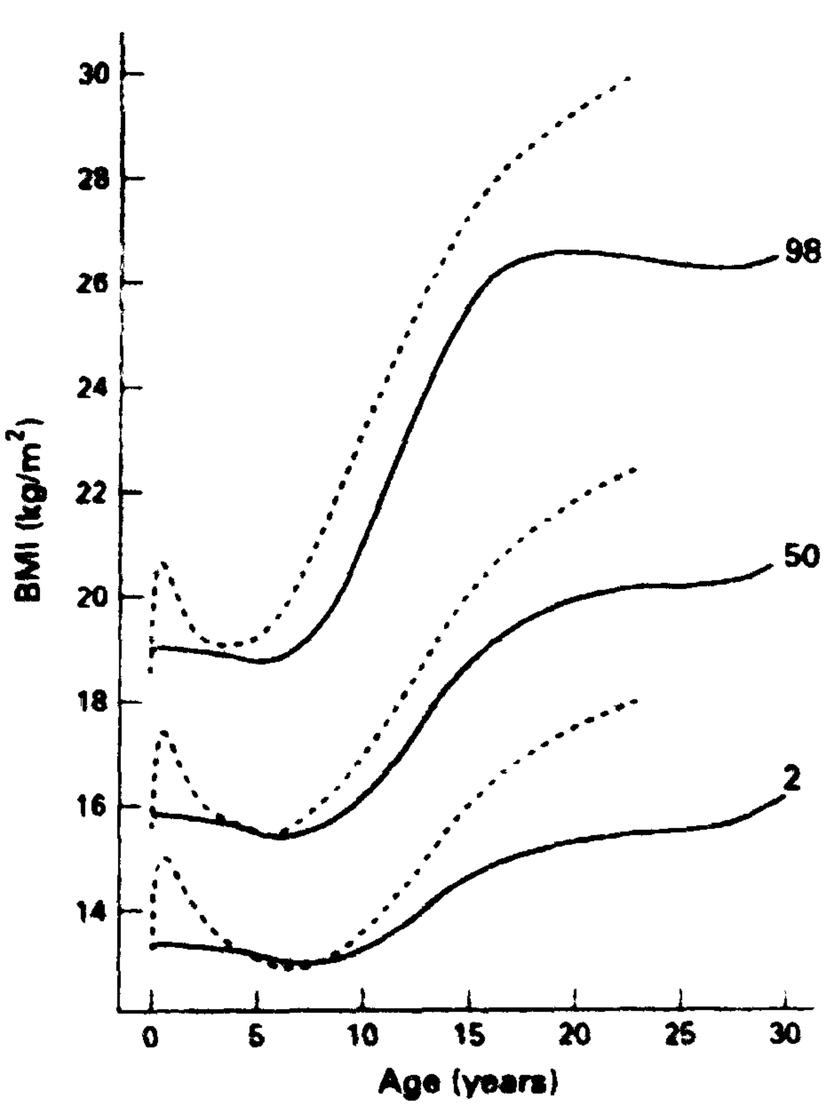
Malabsorption of fat, due to pancreatic insufficiency, is said to be the major primary abnormality with nutritional consequences (Elborn & Bell 1996). In infancy, failure to thrive and steatorrhoea may be the signs leading to the diagnosis of cystic fibrosis. The development of pancreatic enzymes (Littlewood 1996) led to a change in nutritional management from a diet of low fat and high calorie to high fat and high energy intake, with additional enzyme supplementation to counter steatorrhoea. Pancreatic enzyme replacement therapy can clinically correct malabsorption in these patients, but many continue to have evidence of maldigestion and consequent malabsorption (Elborn & Bell 1996).

The BMI is a measure of a person's 'fatness' (Prentice 1998) and is derived from values of both weight and height. It is said to be less affected by differences in the timing of puberty than simple height and weight charts (Prentice 1998). The BMI is the weight in kilograms divided by the square of the height in metres and is therefore a unit of kilograms / metres^2.

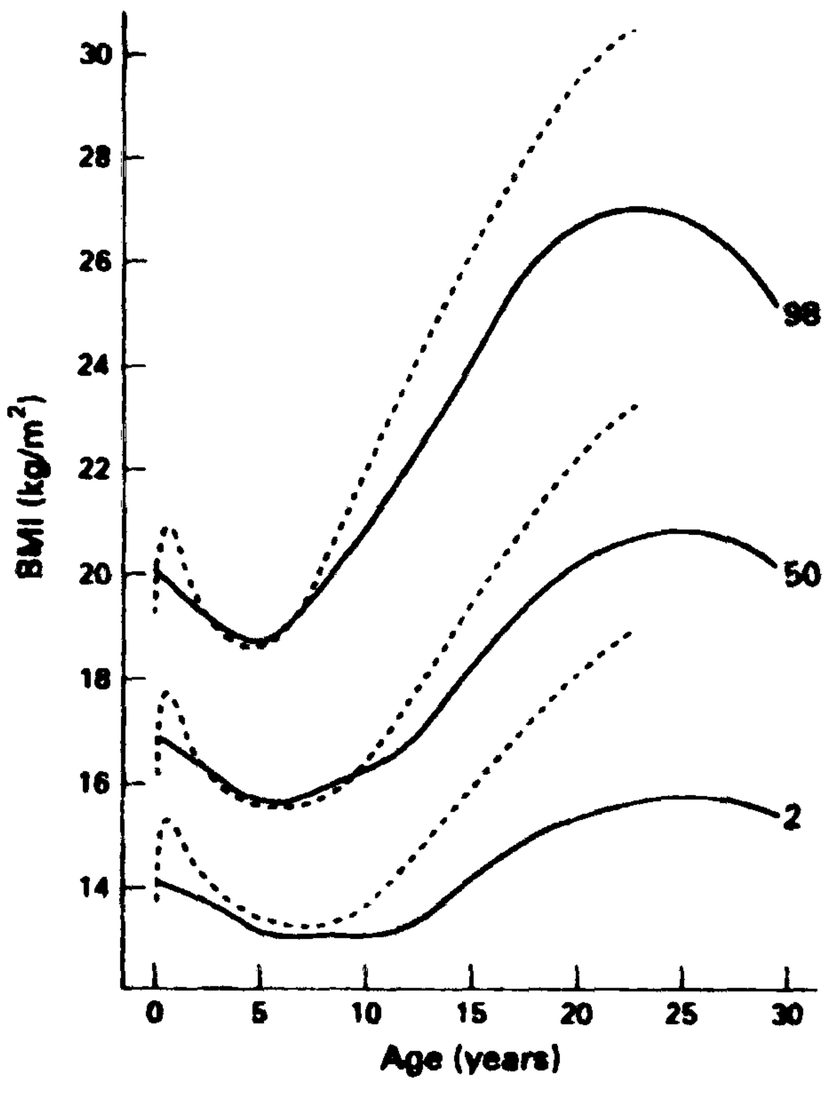
Body mass index categories are said to be (Prentice 1998):

- Underweight: < 18.5 kg/m^2
- Ideal: 18.5 – 24.9 kg/m^2
- Pre-obese class I: 30.0 – 34.9 kg/m^2
- Obese class II: 35.0 – 39.9 kg/m^2
- Obese class III: >40 kg/m^2.

Morison *et al* (1997) calculated the reference centiles for BMI in females (Figure 4.3a) and males (Figure 4.3b) with cystic fibrosis:



4.3a. Females.



4.3b. Males.

Figures 4.3a and 4.3b show the body mass index (BMI) reference centiles (2^{nd}, 50^{th} and 98^{th}), the solid lines, and the British 1990 reference centiles for comparison, the broken lines. There appear to be differences in BMI between females and males. From the age of about 20 years the BMI tends to decrease in men, but to plateau or increase in women. From: Morison *et al* 1997.

Obesity, in the general population, is associated with a decrease in lung function in both children (Li *et al* 2003) and adults (Bottai *et al* 2002; Canoy *et al* 2004). In people with cystic fibrosis it is low body weight which is associated with reduced lung function (Bell *et al* 1998; Nir *et al* 1996; Peterson, Jacobs, Jr., & Milla 2003) and increased mortality (Corey *et al* 1988; Sharma *et al* 2001). There is also a difference in perception of body weight and consequent nutritional behaviour between women and men with cystic fibrosis. The young women tend to overestimate their actual weight and young men to underestimate their actual weight (Walters 2001).

There is well documented evidence of an inverse relationship between weight and mortality in people with cystic fibrosis, but it is not yet clear whether it is the decline in lung function which affects nutritional status or vice versa (Elborn & Bell 1996).

Exercise capacity

Exercise testing can be used to assess a patient's exercise capacity, which cannot be predicted from baseline lung function tests (Ambrosino 1999). In patients with cardiopulmonary disease, exercise testing gives some insight into the circulatory component which may cause exercise limitation (Ambrosino 1999). The exercise test can also be used to prescribe an appropriate exercise programme for an individual (Singh *et al* 1994) and longitudinal measurements allow monitoring of disease progression.

Moorcroft, Dodd and Webb (1997) identified that people with cystic fibrosis and mild to moderate lung function were able to maintain their peak oxygen uptake in spite of a decline in forced expiratory volume in one second (FEV_1). Freeman *et al* (1993) demonstrated that with increasing severity of disease, in adults with cystic fibrosis, maximal exercise capacity may be limited but endurance capacity at the same relative work load is unimpaired.

The disability associated with cystic fibrosis cannot be predicted with accuracy from lung function measurements alone and inclusion of the measurement of exercise capacity will help to quantify the disability objectively (Webb, Dodd, & Moorcroft 1995). The 'gold standard' for all populations is the formal laboratory test with on-line analysis of expired air (Bradley *et al* 2000), but field exercise tests including the six-minute walking test (Butland *et al* 1982) and shuttle tests (Bradley *et al* 1999a; Singh *et al* 1992) are simple, easy to perform, require minimal time, space and equipment, and have general applicablility (Ambrosino 1999).

The twelve-minute walking test was one of the first to be used in respiratory disease (McGavin, Gupta, & McHardy 1976). In a group of people with chronic bronchitis, the distance covered did not correlate with forced expiratory volume in one second, but was significantly related to forced vital capacity and maximum oxygen consumption and ventilation, on a bicycle ergometer. Work by Butland *et al* (1982) showed that the time for the test could be reduced to six minutes. Two practice walks are required with these tests (Butland *et al* 1982) owing to the training effect between tests one and two.

The twelve- and six-minute walking tests are self paced tests and disadvantages include patient motivation, supervisor encouragement, the non-standardised nature of the test (including unrecorded rest periods) and dependence on a single quantitative measure of distance covered (Ambrosino 1999). Guyatt *et al* (1984) demonstrated that simple encouragement improved performance in these tests. They emphasised the importance of careful standardisation. The six-minute walking test has been used in people with cystic fibrosis and Chetta *et al* (2001) suggested that it may be valuable for identifying patients who might experience oxygen desaturation and dyspnoea during demanding daily activities.

The incremental shuttle walking test (Singh *et al* 1992) is an externally paced, standardised incremental and progressive exercise test, derived from the 20-metre shuttle run test of Léger and Lambert (1982). It can be used to measure maximal exercise capacity and as the test is externally paced, it allows valid intersubject and intrasubject comparison. Subjects who achieve 500 metres on the shuttle walking test will have experienced a similar 'work rate / stress' level, but the same comparison cannot be made between subjects or within subjects who have completed 500 metres on the six-minute walking test. The defined speeds of the walking on the shuttle test ensure

that the work load increases incrementally and quantitatively. Singh *et al* (1992) found a significant relationship between the distance walked in the six-minute walking test and the shuttle walking test, but the six-minute walking test appeared to overestimate disability in some patients. Maximal heart rates were significantly higher for the shuttle walking test and the shuttle test provoked a graded cardiovascular response.

The shuttle walking test was originally validated in people with chronic obstructive lung disease, excluding those with cystic fibrosis. From reproducibility studies (Singh *et al* 1992), there is said to be a significant difference between walks one and two but not between walks two and three, suggesting a small training effect. Singh *et al* (1992) recommend one practice walk for the shuttle walking test.

The shuttle walking test has been used as a clinical outcome measure in people with cystic fibrosis (Brown *et al* 2000), but an increasing number of people with cystic fibrosis are physically very fit, for example rugby or football players and skiers. The shuttle walking test does not stress these people and is therefore not a measure of maximal exercise capacity. For many of the women with cystic fibrosis, who are physically fit, it is their stride length when walking rather than their maximal exercise capacity which limits the time and distance of the test. In preliminary studies, Bradley (1998) demonstrated that the shuttle walking test did not elicit a peak exercise response in adults with cystic fibrosis, both those with minimal disability and those with more severe disability.

Modified shuttle test

Bradley et al (1999a) modified the shuttle walking test and validated the modified test, the modified shuttle test (MST), in adults with cystic fibrosis. This work had been accepted for publication, but had not been published at the time of setting up the protocol for the airway clearance study. The original shuttle walking test was modified by the addition of three levels and by permitting the subjects to run. Studies demonstrating the reliability, repeatability and sensitivity of the modified shuttle test, in adults with cystic fibrosis, have been undertaken (Bradley *et al* 2000).

The equipment required is a cassette player and two markers. The modified shuttle test comprises 15 levels. The shuttle walking test has 12 levels. The first speed of walking is known as level 1 and the second as level 2, continuing up to level 15, with each level lasting for one minute. The number of shuttles (10-metre lengths) in each level is dictated by the speed of the level. There are 3 shuttles in the first level, four in the second, five in the third level etc (Appendix 1).

The modified shuttle test requires the patient to walk, and then to jog or run, up and down a 10-metre course. The course is identified by two cones inset 0.5 metres from either end, to avoid the need for abrupt changes in direction (Figure 4.4).

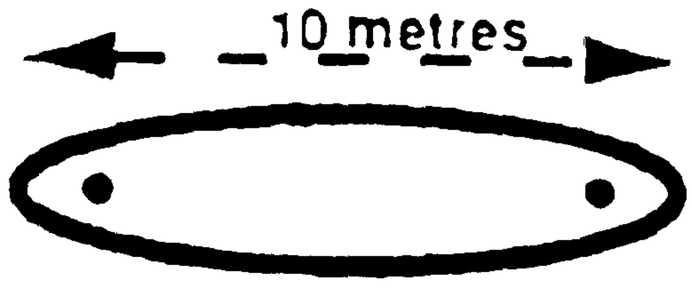


Figure 4.4: The 10-metre shuttle. From: Singh *et al* 1992.

The speed is dictated by a pre-recorded audio signal on a cassette recorder. The tape includes a calibration period of one minute, to ensure accuracy of the timed signal. This tape can be purchased from the Department of Respiratory Medicine, The Glenfield Hospital, Leicester LE3 9QP.

The explanation to the patient has been standardised and is played, from the tape, at the start of each test. The modified shuttle test instructions are based on the shuttle walking test instructions. The patient is told: 'You should walk at a steady pace, aiming to turn around the cone at one end of the course when you hear the first bleep and at the other end when you hear the next.... You should follow the set rhythm for as long as you can breaking into a run when you need to, to maintain the required speed.... You should stop only when you become too breathless to maintain the required speed or can no longer keep up with the set pace.'

The start of the test is indicated by a triple bleep. Thereafter the tape emits a single bleep at regular intervals. At the time of each bleep the subject should be turning round the cone to proceed back down the course. Each minute the speed is increased by a small increment and the subject is therefore required to move progressively faster. A change of speed to the next level is indicated by a triple bleep.

It is recommended that the operator walks alongside the subject, for the first minute, to establish the very slow walking speed of level 1 (Singh *et al* 1992). The subject has 20 seconds to complete each of the three shuttles of level 1. From this point on, the subjects pace themselves by co-ordinating their speed with the timed signals. If a subject reaches the cone before the signal, he/she is instructed to remain at the cone until the signal indicates that he/she should proceed. After the first minute the operator sits alongside the course and no encouragement is given. The only verbal contact is advice to increase the speed slightly at each minute (with the words 'a little faster now'), at the time of the triple bleep signal when a new level is reached, and to remind the subject that he / she can run at any time during the test. The initial speed is 0.5 metres per second (1.12 miles per hour), increasing by 0.17 metres per second for each level (Table 4.1).

The test is ended:

1. By the subject when he / she is too breathless to maintain the required speed or
2. By the operator if the subject fails to complete a shuttle in the time allowed (i.e. is more than 0.5 metres away from the cone when the bleep sounds).

The chart used for recording the shuttles is reproduced in Appendix 1.

Modified Shuttle Test (MST)			
Level	**Distance** (metres)	**Speed** (miles per hour)	**Number of shuttles per level**
1	0 – 30	1.12	3
2	40 – 70	1.50	4
3	80 – 120	1.88	5
4	130 – 180	2.26	6
5	190 – 250	2.64	7
6	260 – 330	3.02	8
7	340 – 420	3.40	9
8	430 – 520	3.78	10
9	530 – 630	4.16	11
10	640 – 750	4.54	12
11	760 – 880	4.92	13
12	890 – 1020	5.30	14
13	1030 – 1180	5.63	15
14	1190 – 1340	6.00	16
15	1350 - 1510	6.38	17

Table 4.1: Modified Shuttle Test. Levels 1 – 12 (Singh *et al* 1992), Levels 13 – 15 (Bradley *et al* 1999a).

Bradley *et al* (1999a) found a strong relationship between peak oxygen consumption and the modified shuttle test (Figure 4.5) with 90% of the variation of directly measured peak oxygen consumption explained by the variation in performance on the modified

shuttle test. This is evidence of criterion-related validity of the modified shuttle test as a measure of exercise capacity in adults with cystic fibrosis.

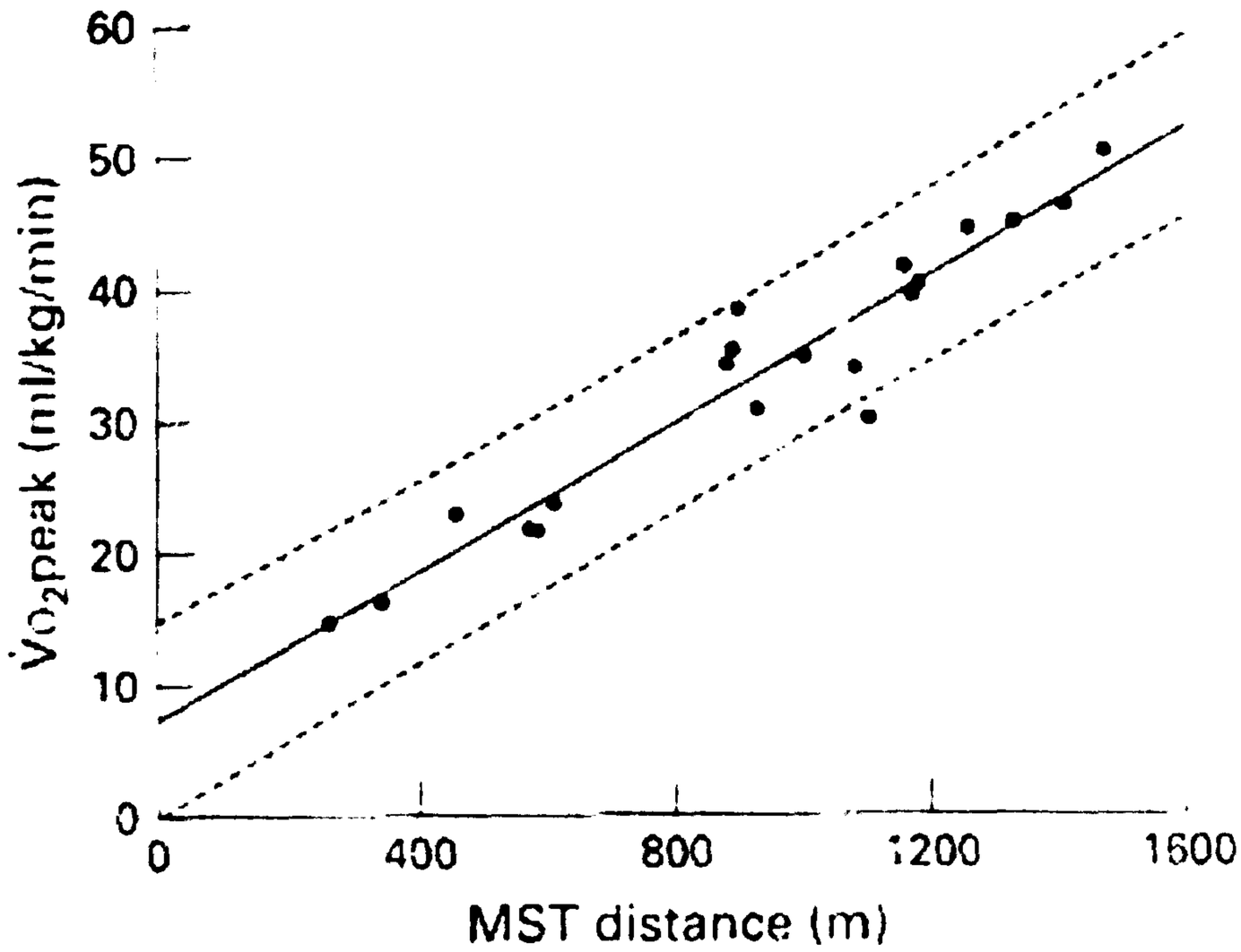


Figure 4.5: The regression line (with 95% confidence intervals) for the relationship between performance (distance in metres) on the modified shuttle test and peak oxygen consumption (Vo_2 peak) measured during treadmill testing. From: Bradley *et al* 1999a.

Hunter *et al* (2000) compared the modified shuttle test with the shuttle walking test, in 15 people with cystic fibrosis. There was a significant correlation between the two tests ($r=0.78$, $p<0.001$), but a significantly greater distance was covered when the subjects were on the modified shuttle test. Not surprisingly, the subjects were more breathless following the modified shuttle test ($p=0.003$) and their perceived exertion was significantly higher ($p=0.002$). Following the modified shuttle test, the drop in oxygen saturation was greater ($p=0.005$). Hunter *et al* concluded that the use of the modified shuttle test had little advantage over a normal walking test and caused greater stress in terms of breathlessness and desaturation. They had previously validated the shuttle walking test in people with cystic fibrosis (Brown *et al* 2000). In the comparison of the

two tests (Hunter *et al* 2000), the predicted FEV_1 of the 15 subjects ranged from 18% to 85% with a median of 37%. For the patients who were less fit, the shuttle walking test should have exercised them to their maximum capacity, but it is unlikely that the very fit ones would have reached this level.

The minimum amount of change to be of clinical importance in the modified shuttle test has been calculated (Bradley *et al* 2000). It is said that performance on the modified shuttle test must improve by more than 4 shuttles (> 40 metres). This ensures that any change is not related to measurement error in the instrument. It has also been demonstrated that a practice walk is not necessary in people familiar with the modified shuttle test (Bradley *et al* 2000), which reduces the time required to use the test in both clinical and research practice.

Oximetry

Pulse oximetry provides a simple, non-invasive and rapid estimate of the gas exchange function of the lungs. It may be used as a continuous measurement or for absolute values, but it does not give any information on arterial carbon dioxide or acid-base balance. Pulse oximetry measures the percentage of oxygen saturation of haemoglobin (SpO_2) that is the amount of oxygen reversibly bound to haemoglobin in arterial blood. Arterial blood gas analysis is considered the gold standard for measuring arterial oxygen, but it is an invasive procedure.

Pulse oximetry utilises the light absorption properties of haemoglobin. This is based on the Beer-Lambert Law that in order to determine the relative absorbance for each of a number of solutes, the transmission of an equal number of light wave-lengths through

the solution must be measured (Jensen, Onyskiw, & Prasad 1998). The equipment consists of a probe with two light emitting diodes (LED) and photodetector, and a microprocessor with display components. The photodetector electronically resolves the output from the diodes into alternating and direct currents. The alternating current detects absorption due to the pulsating component in the tissues and arterial blood vessels. The direct current detects absorption due to non-arterial blood and tissues.

The direct current part is electronically discarded and the alternating current part is processed further. Different amounts of light are absorbed by oxyhaemoglobin (haemoglobin saturated with oxygen) and reduced haemoglobin. The oximeter measures the relative absorption of red light at 660 nanometres and infrared light at 940 nanometres, by oxyhaemoglobin and haemoglobin. At these wavelengths oxyhaemoglobin and haemoglobin allow different amounts of light to pass (oxyhaemoglobin absorbs infrared light and reduced haemoglobin absorbs red light). Pulsatile arterial blood during systole causes an increase in oxyhaemoglobin to the tissues, more infrared light is absorbed and less reaches the photodetector. The calculation of arterial oxygen saturation is based on the changes in optical density associated with systole. The oximeter can convert this relative light intensity information into oxygen saturation and the pulsatile signals can be used to measure the pulse rate. A liquid crystal display presents the data. For accurate recordings, most pulse oximeters require a pulse pressure of more than 20 mmHg (Falconer & Robinson 1990).

The output can be averaged over a fixed number of seconds, for example a three-, six- or twelve-second time interval. This results in a rapid response time interval and stable readings. A fast averaging time is required during exercise studies and the use of three

seconds is said to be appropriate (Kendrick 2001). However the shorter the signal averaging time, the greater the amount of artefact encountered in the recorded signal.

The calculation methods for the displayed values on the Pulsox-3i (Minolta) are:

- For oxygen saturation: the value is obtained by performing moving averaging for the last five seconds and this is updated and displayed every second.
- For pulse rate: the value is obtained by performing moving averaging for the last eight pulse rates and this is updated and displayed every second.

The pulse oximeter is most accurate in the 80% to 100% saturation range, and in this range is said to have an accuracy of 2 percent (± 1SD) (Jensen, Onyskiw, & Prasad 1998; Kendrick 2001). Estimates below 70% are said to be relatively inaccurate and may be as much as ± 10% with a tendency to under-read (Jensen, Onyskiw, & Prasad 1998; Kendrick 2001).

The accuracy of pulse oximetry during exercise is said to be variable (Gaskin & Thomas 1995; Hansen & Casaburi 1987; Mengelkoch, Martin, & Lawler 1994; Ries, Farrow, & Clausen 1985), but the studies by Hansen and Casaburi, and Ries *et al* were undertaken in the 1980's with the older generation of pulse oximeter.

A probe, clip-on or adhesive, reusable or disposable is placed on a site with an adequate pulsating vascular bed, for example finger, ear lobe, toe, nose or forehead. Different sizes are available for neonates, children and adults. The finger probe may be the most accurate (Clayton *et al* 1991; Jensen, Onyskiw, & Prasad 1998; Mengelkoch, Martin, & Lawler 1994) and most finger probes are spring mounted to reduce motion artefacts. The sensitivity to motion artefacts differs among oximeters (Langton & Hanning 1990)

and recent work by Yamaya *et al* (2002) recommends the use of the forehead sensor during maximal exercise.

Nail polish has been shown to interfere with oximetry (Cote *et al* 1988) and should be removed before oximetry monitoring. An overestimation may be caused by carboxyhaemoglobin and hyperbilirubinaemia (Jensen, Onyskiw, & Prasad 1998). An underestimation may be caused by methemoglobinaemia, methylene blue, reduced vascular pulsations, anaemia, skin pigmentation, reduced perfusion, motion artefact, ambient light and malpositioning (Jensen, Onyskiw, & Prasad 1998). Hypoxaemia will magnify the error (Jensen, Onyskiw, & Prasad 1998). The pulse oximeter may fail to record accurately during severe or rapid desaturation and if the subject is hypotensive or hypothermic (Jensen, Onyskiw, & Prasad 1998).

Calibration of pulse oximeters is not easy and it is generally accepted that *in vivo* calibration need take place only during the design and development of the instrument (Kendrick 2001).

In clinical practice it is important to remember that the relationship between oxygen saturation as measured by oximetry and the partial pressure of arterial oxygen is not linear (Figure 4.6).

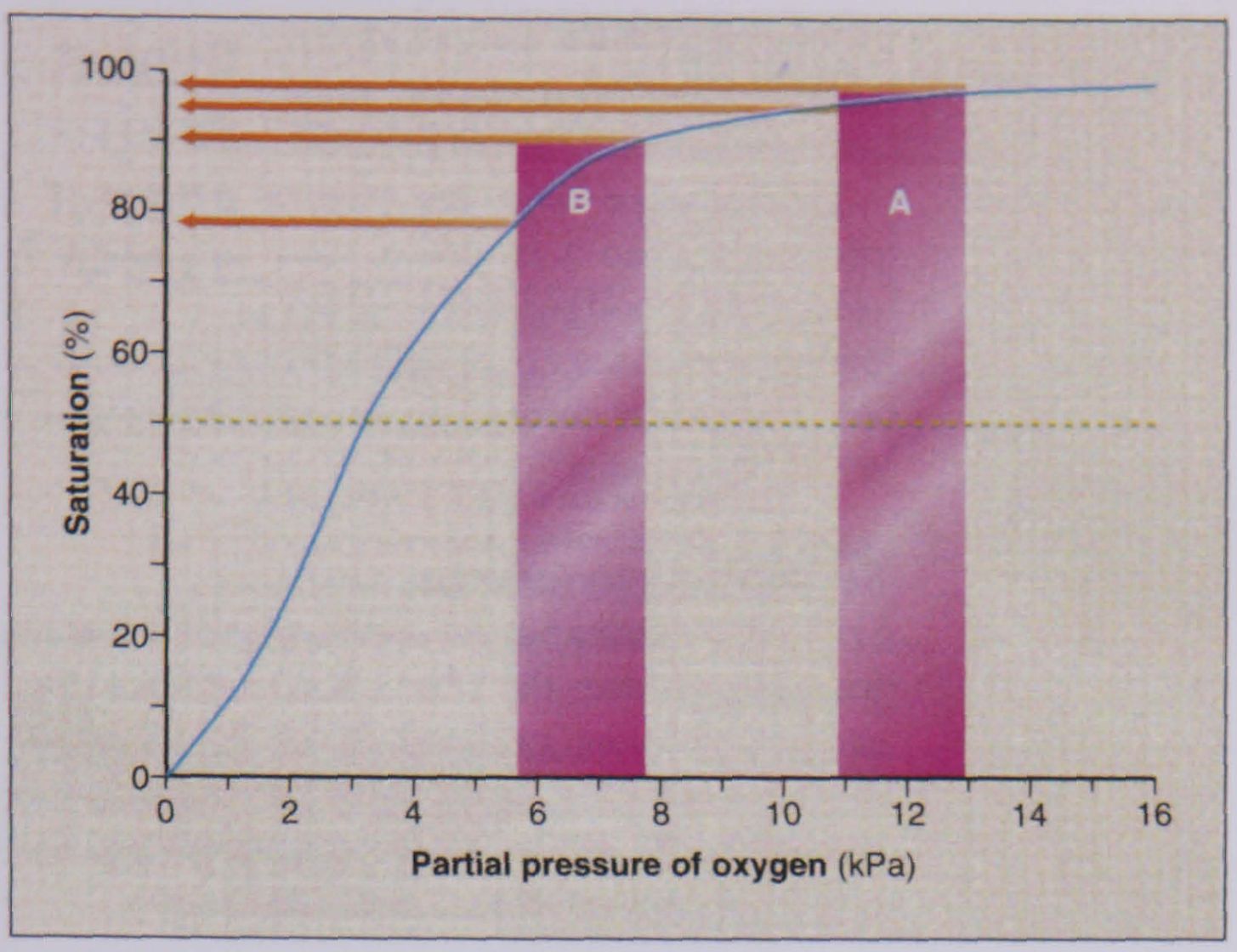


Figure 4.6: The oxyhaemoglobin dissociation curve showing the relationship between oxygen saturation and the partial pressure of oxygen. In 'normal' lungs the shaded area (A) demonstrates that a small change in saturation is seen for a large change in the partial pressure of oxygen, but below 90% (shaded area (B)) the change in saturation is much greater for the same magnitude of change in the partial pressure of oxygen. From: Kendrick 1999/2000.

The Pulsox-3i (Minolta) (Figures 4.7 and 4.8) was selected for the study for its accuracy, affordability and portability. Its specifications are:

- SpO_2 (%) measuring range 0 – 100. Measuring accuracy ±2% (70-100)
- Pulse rate (bpm) measuring range 20 – 250. Measuring accuracy ±2 bpm
- Memory function 12 hours
- Weight 42 grams.

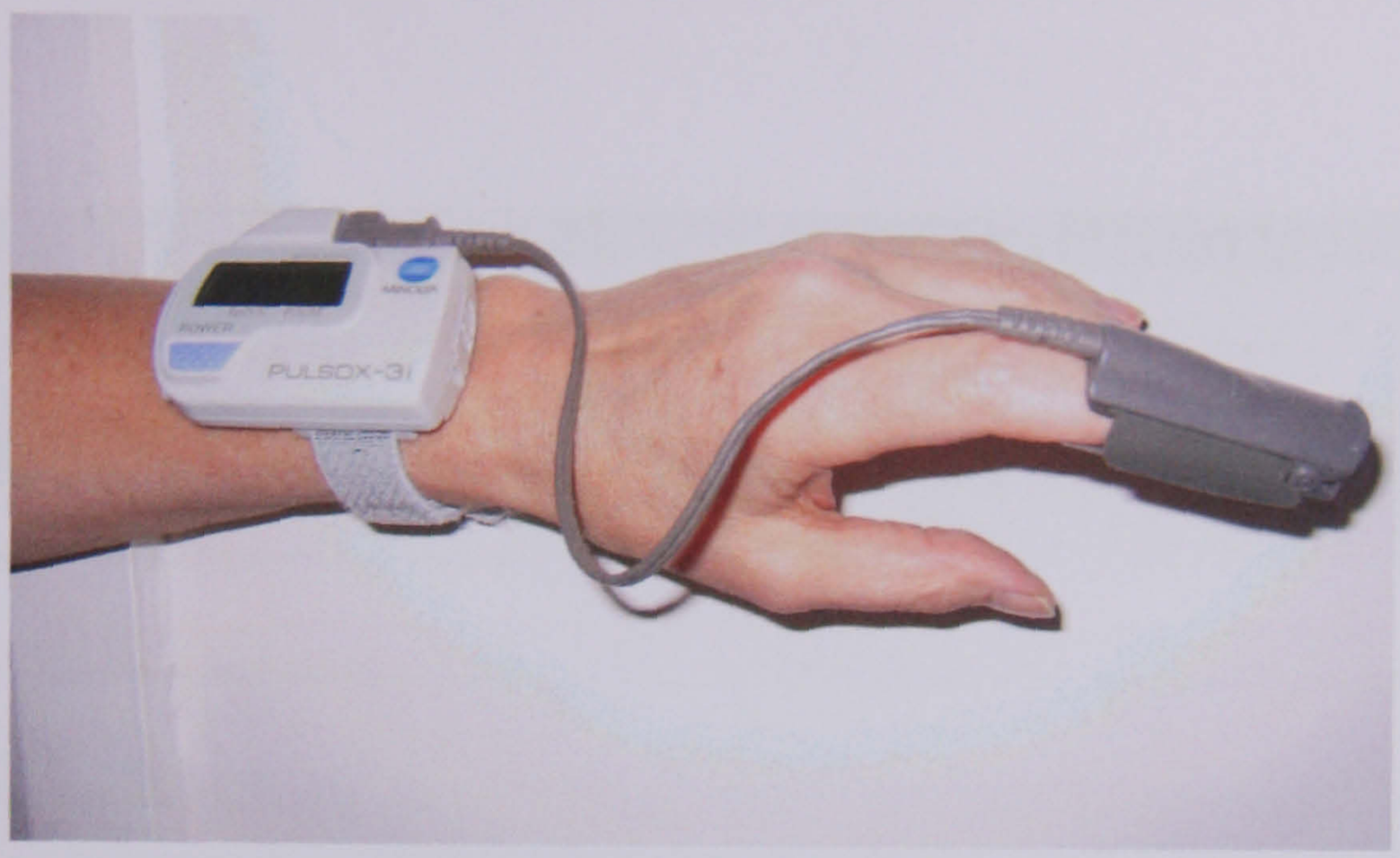


Figure 4.7: Pulsox-3i.

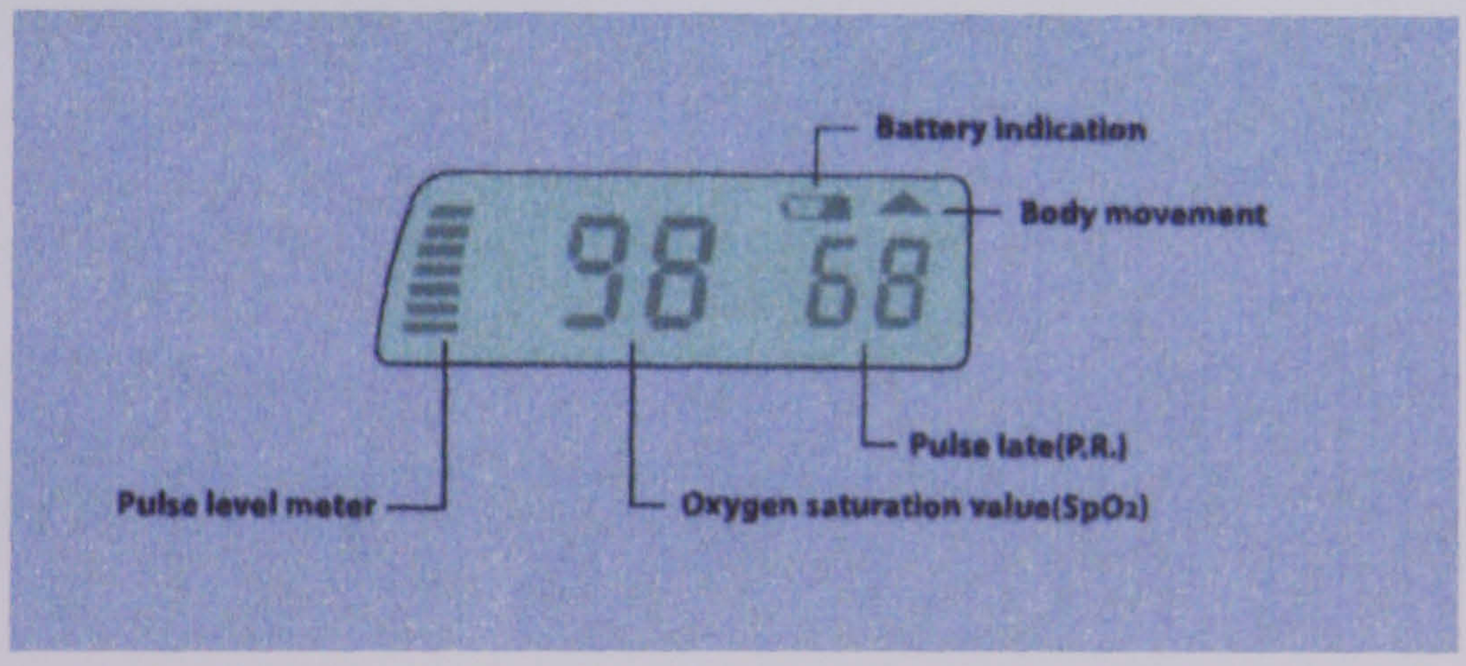


Figure 4.8: The visual display on the Pulsox-3i. Clockwise from the top: Battery indication, Body movement, Pulse rate (PR), Oxygen saturation value (SpO_2) and Pulse level meter.

When the data is downloaded to a computer it can be displayed graphically (Figure 4.9).

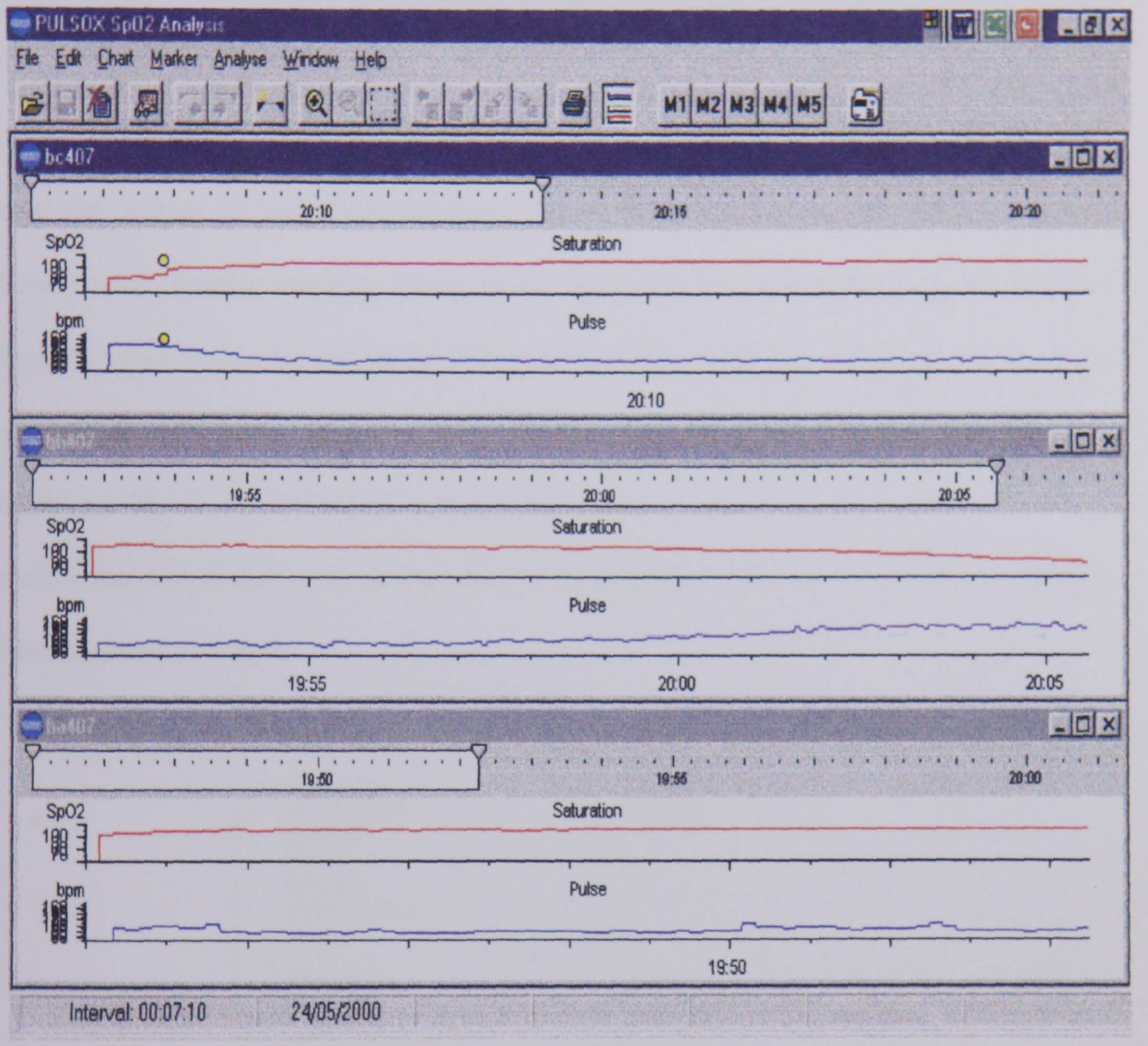


Figure 4.9: Download from the Pulsox-3i showing oxygen saturation (red lines) and pulse rate (blue lines). The bottom graph shows baseline values, for subject 407, before starting the modified shuttle test (MST), the middle graph demonstrates the fall in oxygen saturation and rise in pulse rate during the MST and the top graph shows the increase in oxygen saturation and fall in pulse rate on stopping the MST.

Borg scale

Borg described perceived exertion as the single best indicator of the degree of physical strain (Borg 1982). Perceived exertion is said to integrate information from signals elicited from peripheral working muscles and joints, from central cardiovascular and respiratory functions and from the central nervous system (Borg 1982). Borg's 15-grade scale for ratings of perceived exertion, the RPE scale, was constructed to increase linearly with exercise intensity (Borg 1970). From the 15-grade scale Borg developed a category scale with ratio properties (Borg 1982). This scale has 12 points, 10 of which have verbal descriptors (Figure 4.10). From the scale where for example '2' represents 'weak' or 'light', '1' is half of that represented by 'very weak' or 'very light'. Borg foresaw the use of this scale to include the assessment of subjective symptoms such as breathlessness and pain.

0	Nothing at all	
0.5	Very, very weak	(just noticeable)
1	Very weak	
2	Weak	(light)
3	Moderate	
4	Somewhat strong	
5	Strong	(heavy)
6		
7	Very strong	
8		
9		
10	Very, very strong	(almost max)
•	Maximal	

Figure 4.10: Borg's category scale with ratio properties – the modified Borg scale. From: Borg 1982.

Wilson and Jones (1989) found a significant correlation between the modified Borg scale and minute ventilation. They have said that this indicated that breathlessness was closely related to ventilation, but they noted large inter-subject variations. They hypothesised that this may be due either to the subject's varying sensitivities to the sensory inputs provoking the sensation of breathlessness or to the manner in which the

subjects used the scale. Their subjects were 'normal' subjects rather than patients, to avoid any confounding effects due to possible variations in lung function.

Wilson and Jones (1989) had compared the 'modified Borg scale' (sic) with a visual analogue scale. They found that the Borg scale varied to a lesser extent than the analogue scale and correlated more closely with ventilation. It was also the more reproducible measure. This was surprising as breathlessness is a continuous variable and it could be hypothesised that an analogue scale providing a larger number of scoring levels would allow greater precision. Wilson and Jones suggested that their findings may be due to the psychophysical properties of the Borg scale and possibly the use of verbal descriptors.

The Borg scale has an inbuilt ratio bias (Wilson & Jones 1989). Level '5' on the Borg scale, which is half the maximum score, is labelled 'severe' and there is a tendency to restrict scores to the lower half (lower numbers).

Neely *et al* (1992) compared the visual analogue scale and the category ratio scale (CR-10) for the evaluation of leg exertion. Blood lactate levels were used as correlates to sensory perception. The category ratio scale was said to be slightly more efficient and that this may be due to its greater ability to discriminate at high intensity levels.

Bradley *et al* (1999a) used the modified Borg scale for both leg fatigue and breathlessness in people with cystic fibrosis. Both breathlessness and peripheral muscle symptoms should be assessed in tests of exercise capacity as not all breathless patients stop exercising because of breathlessness (Hamilton *et al* 1995).

The scale used in this thesis was that published by Wilson & Jones (1989). 'Just noticeable' is aligned to '0 – nothing at all' using this scale, very very severe (almost maximal) aligned to 9 and maximal aligned to 10.

0	NOTHING AT ALL (just noticeable)
0.5	VERY VERY SLIGHT
1	VERY SLIGHT
2	SLIGHT
3	MODERATE
4	SOMEWHAT SEVERE
5	SEVERE
6	
7	VERY SEVERE
8	
9	VERY VERY SEVERE (almost maximal)
10	MAXIMAL

Figure 4.11: 'Modified Borg scale'. From: Wilson & Jones 1989.

Quality of life

It is comparatively recently that the patient's point of view has been acknowledged and yet it is the patient's perspective of benefit that is crucial in adherence to treatment (Abbott *et al* 1994; Currie *et al* 1986; Passero, Remor, & Salomon 1981). An airway clearance regimen may, in quantitative terms, be effective and efficient but if it does not appeal or cannot be seen to be of benefit to the patient, in the context of optimising quality of life, he/she is unlikely to adhere to treatment.

Quality of life or health-related quality of life refers to the patient's subjective judgement of health status (Hyland 1997) or perspective of well-being. The terms include experiences of illness such as pain, fatigue and disability, and also the broader aspects of the individual's physical, emotional and social wellbeing. These outcome measures can be 'contrasted' (Hyland 1997) with objective physiological measures and frequently add another dimension to understanding disease and disease processes and the impact of disease on the life of an individual. They may be useful in assessing interventions which improve patients' well-being or ability to function, but do not result in changes in forced expiratory volume in one second (FEV_1) or other objective clinical outcomes. They can also be used to describe health outcomes in ways that are meaningful to patients and their families in addition to health professionals (Abbott, Webb, & Dodd 1997).

There is a low to moderate correlation between spirometric values of lung function and health related quality of life (Bradley *et al* 1999b; de Jong *et al* 1997a). This would suggest that the impact of disease or its treatment on health related quality of life cannot

be estimated by measures of disease impairment and therefore needs to be assessed directly (Bradley *et al* 1999b).

Data can be obtained through either unstructured or structured interviews, or self-reported questionnaires. A generic questionnaire can be used with any disease and one of these is the MOS Short Form-36 (SF-36) (Ware, Jr. & Sherbourne 1992). A generic questionnaire may include questions that are irrelevant to a specific disease and omit questions that are relevant, but it will take into account the overall burden of the disease on everyday functioning and emotional well-being (Engstrom *et al* 2001) and not just that related to pulmonary health. A disease specific questionnaire includes only questions that are relevant to a certain disease and tends to be more sensitive to change, for example the Chronic Respiratory Disease Questionnaire (CRQ) (Guyatt *et al* 1987). With sensitivity to change, this type of instrument can be used to assess the efficacy of a treatment intervention.

The subscales of health related quality of life questionnaires highlight the fact that quality of life is not a single entity. The SF-36 has eight subscales and the CRQ has four. Subscales may be considered in terms of the two constructs of physical problems and emotional problems (Hyland 1997). The effects of an intervention or treatment on the constructs will depend on the extent to which it impacts on either the physiological or psychological functioning of the subject.

The Nottingham Health Profile (Congleton, Hodson, & Duncan-Skingle 1996), Sickness Impact Profile (de Jong *et al* 1997a), Quality of Well Being Scale (Orenstein *et al* 1990), Short Form-36 (Gee *et al* 1999a; Yi *et al* 2004) and Chronic Respiratory Questionnaire (Bradley *et al* 1999b; Wolter *et al* 2002) have been identified as useful

health related quality of life instruments in subjects with cystic fibrosis. Engstrom *et al* (2001) and Goldbeck & Schmitz (2001) recommend the use of both a generic and disease specific instrument when assessing health related quality of life, as it is important to identify not only the disease specific effects, but also impact of the overall burden of the disease on everyday functioning and emotional well-being.

In measurements of health status, the term 'minimally important difference (MID)' is used to denote the smallest difference that signifies an important clinical difference in patients' symptoms (Redelmeier, Guyatt, & Goldstein 1996). It is important for a quality of life measure to assess the magnitude of benefit when comparing two or more treatments, to calculate sample size and to make inferences about the number of patients who improved, remained unchanged or deteriorated as a consequence of treatment (Wright 1996).

The minimally important difference must be interpreted with caution regarding generalisability and equivalence (Wright 1996). A different scale may produce a different result. There is also the question as to whether a minimally important difference derived from a group of subjects can be applied to an individual.

Jones (2002) studied the threshold of clinical significance for three widely used health status questionnaires – Asthma Quality of Life Questionnaire, Chronic Respiratory Questionnaire and St George's Respiratory Questionnaire. He concluded that the threshold for both the Asthma Quality of Life Questionnaire and Chronic Respiratory Questionnaire was in the order of 0.5. The probability of clinical significance is demonstrated in the graph (Figure 4.12).

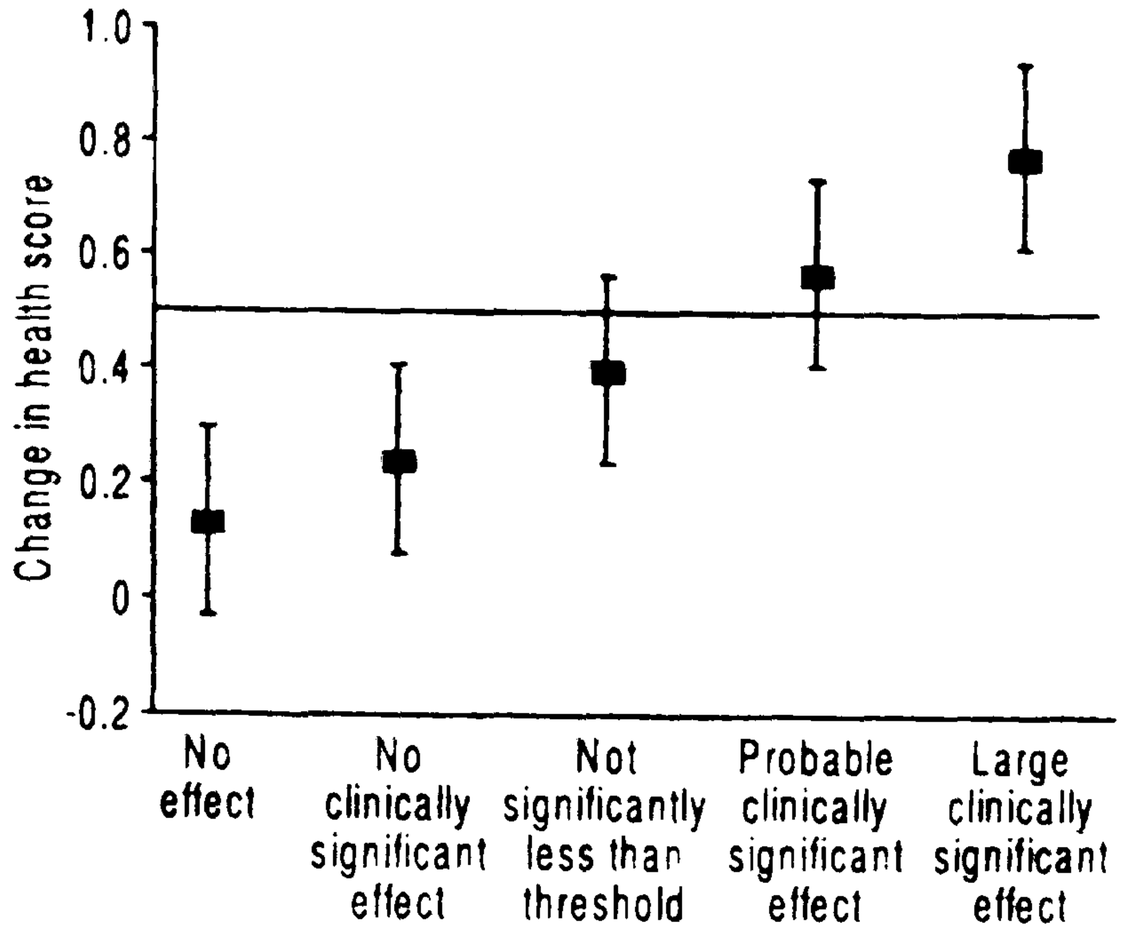


Figure 4.12: The solid lines represent the threshold for a minimum clinically significant effect and the boxes represent 95% confidence intervals. From: Jones 2002.

Norman, Sloan & Wyrwich (2003) showed that a 0.5 standard deviation unit difference or change tended to be minimally important across many studies and instruments, including but not limited to the SF-36. This should be used as a guideline only, as other factors need to be considered before a meaningful change can be said to be valid. These include whether or not the change (Outcomes research analyst 2004):

- Is likely to be due to chance
- Is associated with noteworthy changes in clinical markers
- Is associated with a change in the medical management of the patient
- Moves a patient in or out of the 'normal' range
- Is associated with a change in the patient's evaluation of their health
- Forecasts substantial changes in health-related events e.g. disability, job loss, work productivity, hospitalisation, death.

Validity, reliability and bias of any questionnaire are important. The validity of a questionnaire is expressed in terms of its sensitivity and specificity and is assessed by

comparing a questionnaire's results with independent measurements. The sensitivity of a questionnaire is its ability to detect the known disease in its subjects and its specificity is its ability to identify those without the known disease (Pistelli *et al* 2001) Reliability is expressed as consistency and is measured by the agreement of responses between two administrations of the same questionnaire under conditions assumed not to have changed. The time interval between the two administrations is important. A time interval which is too short may introduce a memory effect and one that is too long risks influence by intervening events (Pistelli *et al* 2001).

Sources of potential bias are said to include the mode of administration (interviewer administered or self-administered) and the questionnaire itself (the wording) (Pistelli *et al* 2001). Interviewer administered may be face to face or by telephone and bias may be introduced by the way in which the questions are presented. Self-administered may be supervised or reviewed by the researcher / clinician. The aim is to maximise validity and reliability and to minimise bias.

Two cystic fibrosis disease specific questionnaires have been published since the airway clearance study of this thesis was set up, but unfortunately they were not in the public domain for use at the time of submission of the study protocol to the Ethics Committee. These are the Cystic Fibrosis Quality of Life (CFQoL) questionnaire (Gee *et al* 2000) and one recently validated in English, the Cystic Fibrosis Questionnaire (CFQ) by Quittner *et al* (2000 & 2004). For the thesis it was decided to take the Short Form-36 (SF-36) as the generic questionnaire and Chronic Respiratory Questionnaire (CRQ) as the disease specific questionnaire, both having been validated in people with cystic fibrosis (Gee *et al* 1999a; Bradley *et al* 1999b).

Short Form-36 questionnaire

The MOS 36 Item Short-Form Health Survey (SF-36) is a generic health related quality of life questionnaire, which allows comparison of data between groups of subjects. The study was registered with Medical Outcomes Trust. Boston. Massachusetts, United States of America (www.outcomes-trust.org) and permission was obtained to use the SF-36 as an outcome measure. The SF-36 has been adapted from the original American version. For the British adaptation only five out of the 36 items required slight modification, for example 'Did you feel full of pep?' (USA) became 'Did you feel full of life?' (UK) and 'Walking one block' (USA) became 'Walking 100 yards' (UK) (Ware, Snow & Kosinski 2000). Other language adaptations / translations are available for Australia and New Zealand, Canada (English and French), Denmark, Germany, Italy, Spain and Sweden.

It is important that the subject completing the questionnaire understands that the process is not a test and there are no right or wrong answers. The questionnaire is for the researcher / clinician and the participant to obtain an appreciation of the general health, from the subject's perspective, of the study population; how well people on the study are able to do their usual activities and how they rate their own health. It is also important that the subject himself fills out the questionnaire and is not influenced by a member of the family or friend who may be present.

The SF-36 has 8 subscales of health concepts (Ware. Jr. & Sherbourne 1992):

- **Physical functioning** - limitations in physical activities because of health problems
- **Role functioning: physical** - limitations in usual role activities because of physical health problems

- **Bodily pain**
- **General health** - perceptions
- **Vitality** - energy and fatigue
- **Social functioning** - limitations in social activities because of physical or emotional problems
- **Role functioning: emotional** - limitations in usual role activities because of emotional problems
- **Mental health** - general mental health (psychological distress and well-being).

The questionnaire is reproduced in Appendix 2. If a respondent omits the answer to a question, the missing value can be estimated using a scoring algorithm. This is the average score across completed items, in the same scale, for the respondent (Ware, Snow & Kosinski 2000). The raw scores are 'transformed' to a 0 to 100 scale (Appendix 3).

The transformation converts the lowest and highest possible scores to 0 and 100 respectively. Scores between these values represent the percentage of the total possible score achieved. The scores are then grouped according to their subscale and a mean value obtained for each subscale.

The meanings of the subscale scores, adapted from (Ware, Snow & Kosinski 2000), are illustrated in Table 4.2.

Subscale	**Low Score**	**High Score**
Physical functioning	Limited a lot in performing all physical activities including bathing or dressing due to health.	Performs all types of physical activities including the most vigorous without limitations due to health.
Role functioning: physical	Problems with work or other daily activities as a result of physical health.	No problems with work or other daily activities as a result of physical health.
Bodily pain	Very severe and extremely limiting pain.	No pain or limitations due to pain.
General health	Evaluates personal health as poor and believes it is likely to get worse.	Evaluates personal health as excellent.
Vitality	Feels tired and worn out all of the time.	Feels full of life and energy all of the time.
Social functioning	Extreme and frequent interference with normal social activities due to physical or emotional problems.	Performs normal social activities without interference due to physical or emotional problems.
Role functioning: emotional	Problems with work or other daily activities as a result of emotional problems.	No problems with work or other daily activities as a result of emotional problems.
Mental health	Feelings of nervousness and depression all of the time.	Feels peaceful, happy, and calm all of the time.

Table 4.2: Short Form-36 subscale scores. From: Ware, Snow & Kosinski 2000.

The eight subscales of the SF-36 can be combined into a physical component summary and a mental component summary (Ware, Jr. *et al* 1995). This reduces the possibility of chance in the hypothesis testing and minimises the 'floor' and 'ceiling' effects. The physical component subscales are: physical functioning, role functioning physical,

bodily pain and general health. The mental component subscales are: vitality, social functioning, role functioning emotional and mental health.

The ability of the SF-36 to discriminate between adults with cystic fibrosis and healthy peers has been reported (Blair, Kacser, & Porteous 1998; Epker & Matt-Maddrey 1999). Gee *et al* (1999a) studied the structure and discriminatory ability of the SF-36 in a group of 225 adults with cystic fibrosis. They concluded that it demonstrated some discriminatory ability as a function of disease severity.

Goldbeck and Schmitz (2001) compared three generic instruments, the SF-36, the quality of life profile for chronic diseases and the questions on life satisfaction, in 70 adolescents and adults with cystic fibrosis (mean age 25.5 years). The SF-36 scored in the upper section of 6 of the 8 subscales. The two exclusions were general health and vitality. The researchers therefore question the discriminative ability of the SF-36 in mild disease. There was a 'ceiling' effect for emotional role functioning and it was concluded that the SF-36 performed best in the physical domains. The recommendation was to use a combination of generic and disease specific instruments.

In the study by Britto *et al* (2002), 48 subjects with cystic fibrosis (mean age 27.1 years) completed the SF-36. Again subjects scored high in role functioning and in the psychosocial domains were similar to the general population without cystic fibrosis, but physical functioning scores were worse. The largest differences in magnitude were seen in the general health perception scale, which was acknowledgement that their state of health was not as good or not likely to be as good as that of their peers who do not have cystic fibrosis. Yi *et al* (2004) identified that acute pulmonary exacerbations affect

physical health related quality of life, but not the psychosocial aspects (as measured by the SF-36 and the Child Health Questionnaire - Parent form).

There is debate as to what constitutes a minimally important difference with the SF-36. QualityMetric Incorporated (Outcomes research analyst 2004) report that five points on a 'norm-based' scale could be considered as meaningful. This is a 0.5% standard deviation unit change or difference at the individual level. For group comparisons the difference is smaller than the recommended difference at the individual level. The 'norm-based' scoring methods used in the scoring of the SF-36 standardise it to have a mean of 50 and a standard deviation of 10 in the 1998 general population (United States of America). The Outcomes research analyst (2004) did not recommend analysis of the data for the minimally important difference.

Chronic Respiratory Questionnaire

The Chronic Respiratory Questionnaire (CRQ) (Guyatt *et al* 1987) is a disease specific health related quality of life instrument (Appendix 4). It can be used for comparison of data within an individual. The original version was in English, but it has now been translated into Danish, Dutch, French, German, Italian, Japanese and Spanish.

As previously identified, at the time of designing the protocol for the study (1998) disease specific instruments for cystic fibrosis had either only recently been developed or were still under development (Gee *et al* 1999b; Henry, Grosskopf, & Aussage 1996; Quittner *et al* 1999; Tullis, Gilljam, & Corey 1999). Since this time disease specific instruments for people with cystic fibrosis have been published as peer reviewed papers (Gee *et al* 2000; Quittner *et al* 2000). The CRQ had been validated in people with cystic

fibrosis by Bradley *et al* (1999b), the paper having been accepted for publication in July 1998.

The CRQ consists of 19 items with four subscales of health concepts (dimensions of quality of life) based on researcher generated domains:

- Dyspnoea
- Emotional function
- Fatigue
- Mastery.

The instrument is a structured interview in the form of a questionnaire. The dyspnoea scale measures dyspnoea when patients are physically active and is individualised for each subject. On first use of the CRQ, the subject is asked to identify activities which have caused breathlessness in the past two weeks. He /she is then asked to identify, and rank, the five that are the most important in their everyday life, but these self-selected activities must be ones which they do frequently and over time. For example skiing may be selected but would not be an activity which could be assessed during the summer months, if the instrument is to be used over a 12-month period. The activities are rated using a numerical 7-point modified Likert Scale, from 1 = extremely short of breath to 7 = not at all short of breath. High scores indicate better health related quality of life.

The dimensions of emotion, fatigue and mastery consist of standard, fixed items with a seven response format (Appendix 5). Responses are graded, for example from 1 = all of the time to 7 = none of the time, or from 1 very dissatisfied, unhappy most of the time to 7 extremely happy, could not have been more satisfied or pleased.

The CRQ pack purchased on registration includes an algorithm for scoring any missing values (Appendix 6).

Scales with a number of response options, for example the seven options of the CRQ, may be more sensitive to longitudinal change (Hyland 1997). The CRQ has been shown to have content validity (Guyatt *et al* 1987, 1989, 1999) and concurrent validity (Guyatt *et al* 1989, 1999; Harper *et al* 1997) but it does not assess restriction of activity or ask questions about cough or sputum. Reliability (Guyatt *et al* 1987; Harper *et al* 1997; Martin 1994; Wijkstra *et al* 1994) and responsiveness (Goldstein *et al* 1994; Guyatt *et al* 1987; Jaeschke, Singer, & Guyatt 1989; Martin 1994; Redelmeier, Guyatt, & Goldstein 1996) have been demonstrated, but these studies have all been in subjects with chronic obstructive pulmonary disease.

Bradley *et al* (1999b), in subjects with cystic fibrosis, demonstrated 'high' internal consistency and 'adequate' construct validity for the dimensions of fatigue, emotion and mastery. There was 'adequate' test-retest reliability, but 'low' internal consistency for the dimension of dyspnoea.

With the CRQ the emotional problem construct is reflected in the emotional function, fatigue and mastery subscales. The physical problem construct is represented in the dyspnoea subscale as the dyspnoea questions are asked in relation to activities.

The technique of informed administration is recommended for the CRQ, to enhance the questionnaire's measurement properties (Guyatt *et al* 1985, 1989). With 'informed' administration, the subject is told his / her previous response before being asked to give the follow up response. The advantage of this is that it provides a point of reference on

which the subject can base his next response. This should increase sensitivity to change, but the disadvantage is that some subjects may wish to demonstrate a positive response and will give an answer that shows some improvement has taken place. This confounding effect will be more significant in studies where the subject cannot be blind to the intervention.

A license agreement is required to use the CRQ. This is via the Licensing Officer (austinp@mcmaster.ca) and on payment of the license fee, a CRQ pack is issued by the Department of Clinical Epidemiology, McMaster University Medical Centre, Ontario, Canada.

The CRQ is scored by adding the scores for each question of each dimension and dividing by the number of questions, for each individual:

- Dyspnoea (Questions 4a – 4e)
- Emotional function (Questions 7, 10, 14 & 16)
- Fatigue (Questions 5, 8, 11, 13, 15, 17 & 19)
- Mastery (Questions 6, 9, 12, 18).

Questions 1 to 3 are used to identify and rank the individualised activities of dyspnoea.

Jaeschke, Singer and Guyatt (1989) identified a mean change in score of approximately 0.5 per item as being the minimally important difference for the CRQ. At a later date Redelmeier, Guyatt & Goldstein (1996) confirmed this finding using an alternative technique and subdivided the differences further: 0.5 is said to represent a small difference in symptoms, 1.0 a moderate difference and 1.5 a large difference.

Diary

All subjects were encouraged to keep a weekly record, including number of airway clearance sessions, approximate length of time of each session, amount of physical exercise, sputum colour, changes in drug regimen and whether or not someone had encouraged them to do their treatment by responding to the following questions (The format of the diary card is reproduced in Appendix 7):

1. In the last week how many treatments do you think you should have done each day?
2. Approximately how many treatments did you miss in the last week?
3. In the last week approximately how long did each of your treatment sessions take?
4. What form of exercise have you taken this week?
5. On how many days did you exercise?
6. Has there been any change in your sputum this week? (Yes / No / If yes, please describe).
7. Have you changed any of your drugs this week? (Yes / No / If yes, please describe).
8. Was someone reminding / encouraging you to do your physiotherapy this week? (With every treatment / With most treatments / With a few treatments / With no treatments).
9. Have you any other comments?

Chapter V. Methodology

While the proposal for the airway clearance study was still in draft form, the Lead Researcher visited and worked with the internationally recognised experts of the different airway clearance regimens:

- Jean Chevaillier, autogenic drainage, Belgium
- Lynne Gumery, autogenic drainage, United Kingdom
- Professor Ulrich Cegla, cornet, Germany
- Jim Bolek, flutter, United States of America
- Mette Kelstrup, positive expiratory pressure, Denmark

(The Lead Researcher is considered one of the proponents of the active cycle of breathing techniques).

The proponents had an opportunity to input to the study design at this stage and were invited to visit the United Kingdom at an appropriate and convenient time, to see two or three of the subjects randomised to their arm of the study.

In addition the draft proposal was discussed with Mrs Fran Ashworth (Dietitian, UK), Mrs Chris Baker (Scandipharm UK), Dr Diana Bilton (Consultant Physician, UK), Dr Judith Bradley (Physiotherapist, UK), Mr Robert Chatburn (Respiratory Therapist, USA), Mr Derek Cramer (Principal Clinical Scientist, UK), Dr Paul Cullinan (Reader, UK), Dr David Currie (Consultant Physician, UK), Mrs Mary Dodd (Consultant Physiotherapist, UK), Professor John Dodge (Consultant Physician, UK), Miss Anna Edwards (Senior Nurse, Infection Control, UK), Dr Hilde Franckx, (Consultant Physician, Belgium), Professor Duncan Geddes (Consultant Physician, UK), Professor David Hansell (Consultant Radiologist, UK), Mrs Bernadette Henderson

(Physiotherapist, UK), Dr David Honeybourne (Consultant Physician, UK), Dr Adrian Kendrick (Consultant Scientist, UK), Dr Richard Knight (Senior Lecturer, UK), Dr Christian Koch (Consultant Physician, Denmark), Dr Michael Konstan (Consultant Physician, USA), Ms Ammani Prasad (Physiotherapist, UK), Dr Pallav Shah (Consultant Physician, UK), Dr David Stableforth (Consultant Physician, UK), Dr Robert Stern (Consultant Physician, USA), Mrs Jackie Turner (Statistician, UK), Ms Cheryl Velotta (Respiratory Technician, USA), Miss Barbara Webber (Physiotherapist, UK) and Dr Peter Wills (Consultant Physician, UK).

All patients registered at Royal Brompton Hospital with cystic fibrosis, diagnosed either by genotype or sweat test (sweat sodium >70 millimols per litre), were eligible to enter the study. The study was approved by Royal Brompton & Harefield NHS Trust and the National Heart & Lung Institute, Imperial College, Ethics Committee (Protocol Reference Number: 99-043).

Inclusion criteria

- Diagnosis of cystic fibrosis (genotype or sweat sodium concentration > 70 mmol/litre)
- Aged 16 years of age or over
- Forced expiratory volume in one second ≥ 25% predicted, on assessment for entry to the study.

Exclusion criteria

- Evidence of a current respiratory exacerbation (as defined by Thornton *et al* 2004) that is an increase in lower respiratory tract symptoms requiring treatment with intravenous antibiotics)

- Past history of pneumothorax
- Current severe haemoptysis
- Awaiting lung / heart-lung transplantation
- Pregnancy
- Recent (within 3 months) acquisition of *Burkholderia cepacia*.

Patients who met the entry criteria, and lived within a commutable distance of London, were invited by letter (Appendix 8) to enter the study. Patients were followed up either when they attended the Outpatient Clinic or by telephone, by the Lead Researcher or the Senior Research Nurse for the Department of Cystic Fibrosis. The study was at the time called 'Should any one airway clearance technique be recommended for people with cystic fibrosis?'

The Lead Researcher discussed the study in detail with patients who expressed an interest, demonstrated the airway clearance techniques the patient was not familiar with and gave the patient the 'Form of Consent' (Appendix 9) with the words written on it 'For information only – not for signing at this stage'. The prospective subject was then given at least 24 hours in which to consider entering the study followed by an opportunity to ask more questions, to decline or to accept the invitation.

Entry to the study was, when possible, arranged to coincide with the patient's annual review to avoid repetition of any tests and questionnaires e.g. full lung function tests, the SF-36 questionnaire and the shuttle test.

Randomisation

The randomisation process had been set up by the Statistician (JT) who had given advice and support before the study was submitted to the Ethics Committee. The randomisation used a random number sequence and was stratified by forced expiratory volume in one second as percent predicted (FEV_1 <50%; $FEV_1 \geq 50\%$) and sputum expectorated (< one cupful per day; ≥ one cupful per day). The Annual Review Nursing Sister held the codes and the Lead Researcher obtained the code for a subject prior to Day 1 of the study. In this way subjects were randomised to one of the five regimens of the active cycle of breathing techniques, autogenic drainage, cornet, flutter or positive expiratory pressure.

The identified regimen was explained to, discussed with and practised by the subject while with the researcher/s. Written instructions were given to each subject with the regimens taken from the approved and signed regimens of the proponents (Appendix 10). When a device was used, cleaning instructions for the device were discussed and given to the subject in writing (Appendix 11). The cleaning instructions had been discussed with, and approved by, the Senior Nurse for Infection Control, Royal Brompton & Harefield NHS Trust.

The treatment regimens were undertaken in the sitting position. In discussion with the Lead Researcher, subjects identified the number of airway clearance sessions that were appropriate at the time of entering the study, but knew to increase the length and frequency of treatments if optimal clearance was not achieved. Treatment times and the number of treatment sessions were individualised, and varied within subjects and between subjects. The diary card was explained and subjects were encouraged to complete this at the end of each week. All subjects were encouraged to continue their

current physical activities.

Acute pulmonary exacerbations of infection were treated using additional physiotherapy techniques if indicated, for example chest clapping and shaking by an assistant and gravity assisted positioning, together with optimal medical management. Subjects were free to either continue their study regimen during an acute infection or to re-start it following the acute episode.

Two physiotherapists, with considerable experience in autogenic drainage and recognised as experts by Jean Chevaillier (Belgium), trained the subjects on the autogenic drainage arm of the study assisted by the Lead Researcher. The Lead Researcher trained the subjects on the other four arms.

Outcome measures

The outcome measures of lung function, body mass index, exercise capacity and quality of life are described in Chapter IV.

- Full lung function studies: The physiologist in the Lung Function Unit was blind to the regimen to which the subject had been randomised. These studies were undertaken at 0 months, 6 months and 12 months and provided the data for the primary outcome measure of forced expiratory volume in one second (FEV_1) and the secondary outcome measures of forced vital capacity (FVC), maximal expiratory flow at 25% of forced vital capacity (MEF_{25}) and residual volume as a percent of total lung capacity (RV%TLC). Predicted normal values were calculated in accordance with standardised lung function testing (Quanjer *et al* 1993).

Quality control is rigorous in the Lung Function Unit at Royal Brompton Hospital. Biological controls are undertaken on a daily basis for each piece of equipment together with the appropriate calibrations. These calibrations are undertaken between each patient. The coefficient of variance is generally about 5 percent in trained normals (Cramer 2004). Audits in this Unit have demonstrated a coefficient of variance of between 2 and 3 percent in trained staff performing routine lung function tests (Cramer 2004). However, the exception to this is for measurements involving airways resistance and residual volume, where the coefficient of variance is slightly higher.

- Body mass index: calculated from the subject's weight and height taken at the time of the full lung function tests (0, 6 and 12 months).

- Spirometry including measures of FEV_1, FVC and MEF_{25}: undertaken by the Lead Researcher at the time of each monthly visit. The best of three technically acceptable manoeuvres (Quanjer *et al* 1993) was taken and if necessary the greatest sum of FEV_1 and FVC was calculated to determine the best flow volume loop. The spirometer was calibrated, using a three-litre syringe before each patient and a biological control used at the beginning of each study day.

- Modified shuttle test with recording of oxygen saturation, and Borg scales of breathlessness and fatigue: undertaken monthly. A practice shuttle was undertaken if the subject was unfamiliar with the test.

For the modified Borg scales, the questions were standardised:

1. Using this scale of 0 – 10, please indicate how breathless you are feeling at this moment.
2. Using this scale of 0 – 10, please indicate how tired your legs are feeling at this moment.

- Chronic Respiratory Questionnaire: completed monthly as recommended by Dr G. Guyatt, using the interviewer technique.

- Short Form-36 questionnaire: completed monthly as recommended by QualityMetrics (United States of America) to correlate with the Chronic Respiratory Questionnaire.

- Diary card (Appendix 7): written up weekly. This provided data for the analysis of time for a treatment session, adherence to treatment and the relationship between adherence to treatment and exercise.

- The data on the number of courses of intravenous antibiotics: obtained from the diary cards and the subjects' medical notes.

At the time of each visit, the subject's airway clearance technique was assessed and corrected if necessary.

Statistical analysis

Sample size calculation was based on the only available data at the time of setting up the study and was from short term airway clearance studies (Pryor *et al* 1979, 1994). For 80% power and 5% level of significance, 16 subjects would be required per group (Turner 1998). Intention to treat was used for the primary outcome measure of forced expiratory volume in one second (FEV_1).

The distribution of the data was analysed using SPSS® statistical analysis software. Exploratory statistical analysis was undertaken using one-way analysis of variance (ANOVA) for the primary outcome measure of FEV_1, to assess any variability among the groups. Z-scores were explored for FEV_1 (where Z = mean for individual regimen – mean for the group [population] / SD for the group [population]).

Mixed model analysis of variance (SAS®) (Brown & Prescott 1999; Littell, Henry, & Ammerman 1998) was used in the formal analysis of the data. This separates out the variance of the time factor and allows multiple comparisons. It allows for a wide variety of ways in which observations are correlated with one another. In this study there were comparisons between two points in time: 0 months and 12 months, and among the five groups: active cycle of breathing techniques, autogenic drainage, cornet, flutter and positive expiratory pressure.

Analysis of variance assumes that residual or error terms are independently and identically distributed (Brown & Prescott 1999). Mixed models allow more flexibility in analysis by taking into account more complicated data structures and allowing 'relaxation' of the assumption of independence (Brown & Prescott 1999). For example

if repeated measurements are made on a subject with treatment and time as two of the factors, mixed model analysis allows examination and comparison of response trends averaged over time (Littell, Henry, & Ammerman 1998).

For time for a treatment session and adherence to treatment, the two-sample test for equality of proportions with continuity corrections was used.

Chapter VI. Results

Four hundred and sixty-three adult patients with cystic fibrosis (aged 16 years and over) were registered at Royal Brompton Hospital in 1999, at the start of the study (Figure 6.1). The diagnosis was either by genotype or sweat sodium of >70 milliequivalents per litre. Of these, 344 patients were within a commutable distance of London or known to be willing to travel to London. Two hundred and eighty-nine theoretically met the entry criteria for the study. These patients were invited by letter to participate. Seven replied and of these four were willing to enter. Five letters were returned 'Address unknown'.

Using the personal approach, as a follow up to the letter, 226 subjects were identified as participating in other studies or having just completed another long term study, too busy especially with work and home commitments (even with evening and weekend appointments being offered), found on assessment to have contra-indications to entry (for example a past history of pneumothorax, an FEV_1 of below 25 percent predicted FEV_1 or pregnant or considering pregnancy), on the transplantation waiting list, not contactable, transferred to another cystic fibrosis centre, not interested or giving no reason for non-participation .

Sixty-three patients entered the study with an additional 12 patients who had been newly referred to Royal Brompton Hospital during the study period. As seen in the trial profile (Figure 6.1) our database of 463, together with additional new referrals to the Hospital, led to 75 subjects being willing to enter the study. Using intention to treat, data was available on 65 of the subjects at the end of the 12-month study period. Fifty-three subjects completed the 12-month study period on the regimen to which they had been randomised.

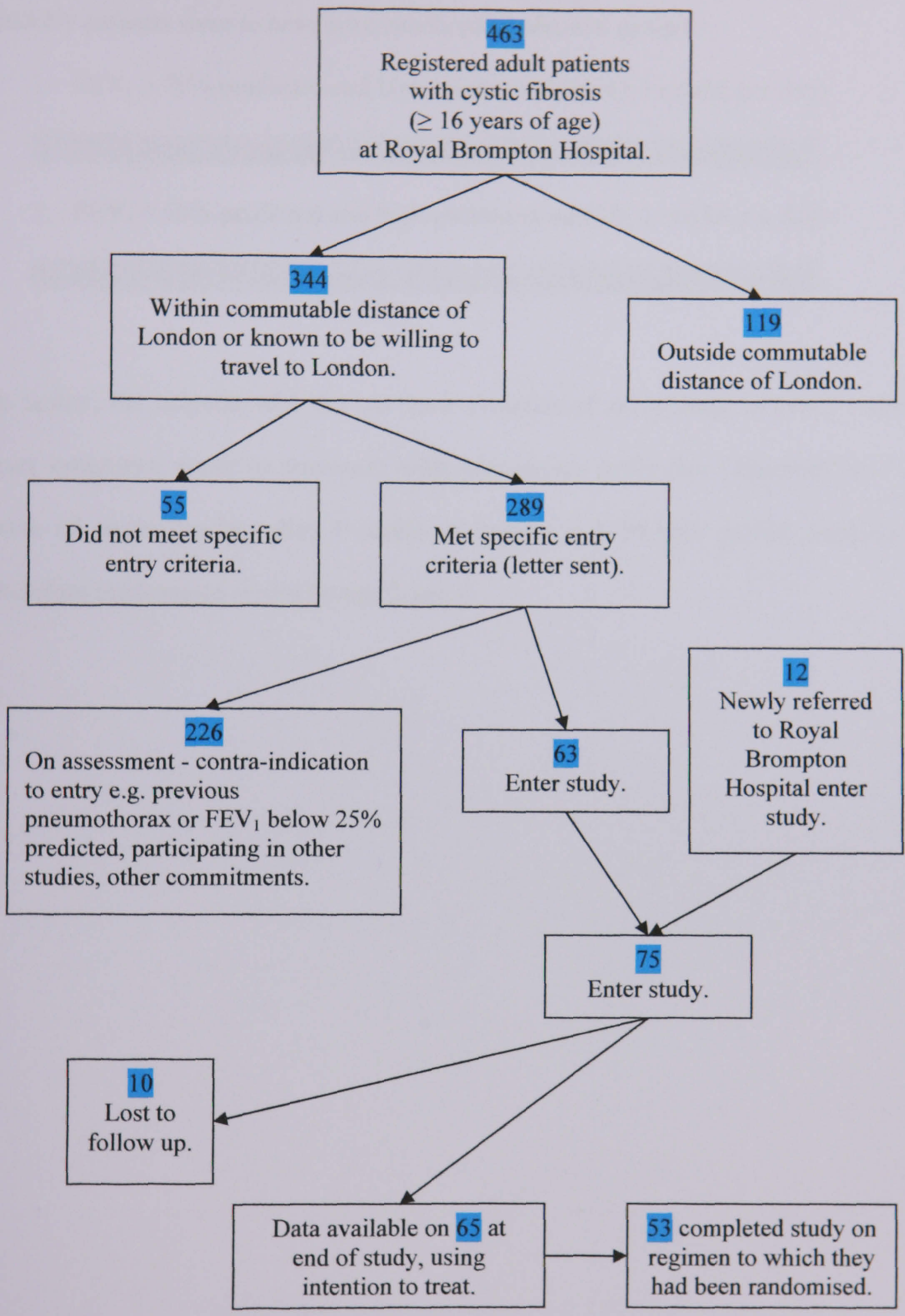


Figure 6.1: Trial profile.

Initially patients were to have been randomised across 4 groups:

1. $FEV_1 \geq 50\%$ predicted and high sputum volume ($\geq$ 1 cupful per day)
2. $FEV_1 \geq 50\%$ predicted and low sputum volume (< 1 cupful per day)
3. $FEV_1 < 50\%$ predicted and high sputum volume ($\geq$ 1 cupful per day)
4. $FEV_1 < 50\%$ predicted and low sputum volume (< 1 cupful per day).

In reality, the subjects who did not have evidence of an increase in lower respiratory tract symptoms requiring treatment with intravenous antibiotics (Thornton *et al* 2004) were all producing less than 1 cupful of sputum in a 24-hour period. Subjects were therefore randomised across groups 2 and 4.

Patient characteristics

The patients' characteristics are summarised in Table 6.1.

	ACBT	AD	Cornet	Flutter	PEP
Age (years) Mean (± SD)	31.1 (± 9.7)	25.9 (± 6.5)	25.3 (± 8.3)	32.1 (± 7.5)	29.3 (± 12.0)
	Range: 17-52	Range: 17-39	Range: 17-49	Range: 19-41	Range: 18-63
Median (± Interquartile range)	30.0 (±16.0)	25.0 (±6.0)	24.0 (±8.0)	34.0 (±13.0)	25.0 (±13.0)
Sex	Male: 11 73.3%	Male: 10 66.7%	Male: 8 53.3%	Male: 10 66.7%	Male: 8 53.3%
	Female: 4 26.7%	Female: 5 33.3%	Female: 7 46.7%	Female: 5 33.3%	Female: 7 46.7%
FEV_1 (litres) Mean (± SD)	2.0 (± 0.8)	2.6 (± 1.3)	1.9 (± 0.8)	2.4 (± 0.9)	2.1 (± 1.1)
Median (± Interquartile range)	1.6 (±1.3)	2.4 (±2.3)	1.7 (±1.2)	2.1 (±1.7)	1.8 (±1.5)
Median value **SpO_2** Mean (± SD)%	96.2 (±1.5)	96.8 (± 2.0)	96.3 (± 1.6)	97.2 (± 1.8)	96.4 (± 1.6)
Median (± Interquartile range)	97.0 (±2.0)	97.0 (±1.8)	97.0 (±3.0)	97.0 (±3.0)	96.0 (±3.0)
Modified shuttle distance (metres) (Mean ± SD)	1005.4 (± 317.0)	985.0 (± 445.9)	906.7 (± 311.5)	1044.3 (± 292.2)	887.9 (± 358.3)
Median (± Interquartile range)	1010.0 (± 445.0)	900.0 (± 445.0)	930.0 (± 350.0)	975.0 (± 520.0)	880.0 (± 597.5)
BMI (weight in kilograms/height in metres^2) (Mean ± SD)	21.1 (± 3.0)	22.6 (± 3.2)	20.9 (± 3.0)	22.8 (± 3.1)	21.5 (± 3.3)
Median (± Interquartile range)	20.5 (±3.7)	22.7 (±4.0)	21.5 (±6.0)	22.8 (±3.2)	20.6 (±4.6)

Table 6.1: Characteristics of the subjects who entered the study (n=75).

The age range of the subjects was from 17 to 63 years. Appendices 12 to 18 summarise the subjects' genotypes (Appendix 12), dominant organisms (Appendix 13), co-existing conditions (Appendix 14), number on Dornase alfa (Appendix 15), pancreatic sufficiency (Appendix 16) and number of new referrals (Appendix 17).

Of the 75 patients who entered the study, 54 completed the six-month assessment and 53 the 12-month assessment. Some of those who were assessed at 12 months had not been available at six months and vice versa. Data from 65 subjects were available for analysis at 12 months using intention to treat.

Of the 22 patients who did not continue the study for 12 months:

- 1 had died (in Australia, after flying to Australia for a holiday) - ACBT
- 1 was withdrawn on being accepted on to the Transplantation Waiting List -AD
- 1 was withdrawn following a limited pleurodesis for a pneumothorax - cornet
- 13 did not like the regimen to which they had been randomised and withdrew, either to revert to their original airway clearance regimen (9) or to a different one of their own choosing (4). From the ACBT regimen three withdrew (two to revert to the use of the head-down tip position), from AD three withdrew, from the cornet two withdrew, from the flutter two withdrew and from PEP three withdrew
- 3 were lost to follow up (ACBT, AD, AD)
- 3 withdrew - 1 giving no reason (cornet), 1 did not wish to undergo any more tests (flutter) and 1 took up a new job outside London (PEP).

Lung function data from 12 of the 22 individuals who did not complete the study was available 12 months following the subject's entry to the study. This was on subjects who had entered the study at the time of their annual review and although they had discontinued the study they were re-assessed with full lung function testing 12 months later. This provided data for an additional 12 subjects to be included in the outcome measures of FEV_1, FVC, MEF_{50}, and RV%TLC using intention to treat.

Lung function

The values for forced expiratory volume in one second (FEV_1) and the percent predicted FEV_1, for each subject on entry to the study, are given in Table 6.2.

FEV_1 in litres for each subject on entry to the study (0 months) (Percent predicted FEV_1 in parenthesis)				
ACBT	**AD**	**Cornet**	**Flutter**	**PEP**
1.18 (23.8)	1.15 (36.5)	2.43 (59.5)	1.94 (42.7)	2.75 (67.2)
1.41 (46.2)	3.09 (74.5)	1.70 (47.8)	1.63 (40.8)	4.48 (98.0)
1.62 (57.8)	1.49 (42.6)	0.83 (27.4)	1.19 (43.7)	0.83 (24.8)
2.50 (50.8)	3.89 (86.0)	2.52 (74.7)	3.36 (90.6)	1.72 (43.4)
2.33 (65.8)	0.84 (26.9)	1.67 (49.6)	2.32 (54.1)	1.39 (40.7)
2.03 (54.1)	3.54 (83.0)	1.34 (40.8)	3.91 (119.6)	2.78 (82.8)
3.03 (72.3)	2.43 (64.0)	2.81 (94.3)	2.39 (55.3)	2.21 (68.8)
1.48 (40.1)	1.88 (57.7)	2.69 (65.7)	1.51 (37.9)	3.46 (82.0)
0.72 (29.2)	2.59 (70.8)	1.58 (54.7)	1.90 (65.1)	1.28 (28.0)
2.80 (71.9)	1.59 (41.5)	1.71 (57.2)	2.12 (52.3)	1.08 (34.4)
1.55 (36.5)	4.56 (103.8)	0.82 (23.8)	2.58 (70.1)	1.22 (56.2)
3.40 (80.5)	4.53 (99.7)	0.67 (21.4)	3.77 (80.3)	1.88 (61.4)
1.50 (39.7)	3.79 (101.1)	1.84 (52.3)	1.69 (55.3)	3.54 (87.5)
2.68 (76.7)	0.88 (32.6)	3.65 (84.9)	3.58 (93.1)	1.75 (40.9)
1.38 (43.6)	2.07 (57.3)	2.44 (47.6)	1.54 (50.3)	1.43 (35.0)
Mean and in parenthesis the standard deviation for FEV_1 in litres				
1.97 (0.77)	2.55 (1.28)	1.91 (0.84)	2.36 (0.89)	2.12 (1.06)
Median and in parenthesis the interquartile range for FEV_1 in litres				
1.62 (1.27)	2.43 (2.3)	1.71 (1.18)	2.12 (1.73)	1.75 (1.50)
Mean and in parenthesis the standard deviation of FEV_1 as percent predicted				
52.60 (17.74)	65.20 (25.89)	53.45 (20.94)	63.41 (23.31)	56.74 (23.52)

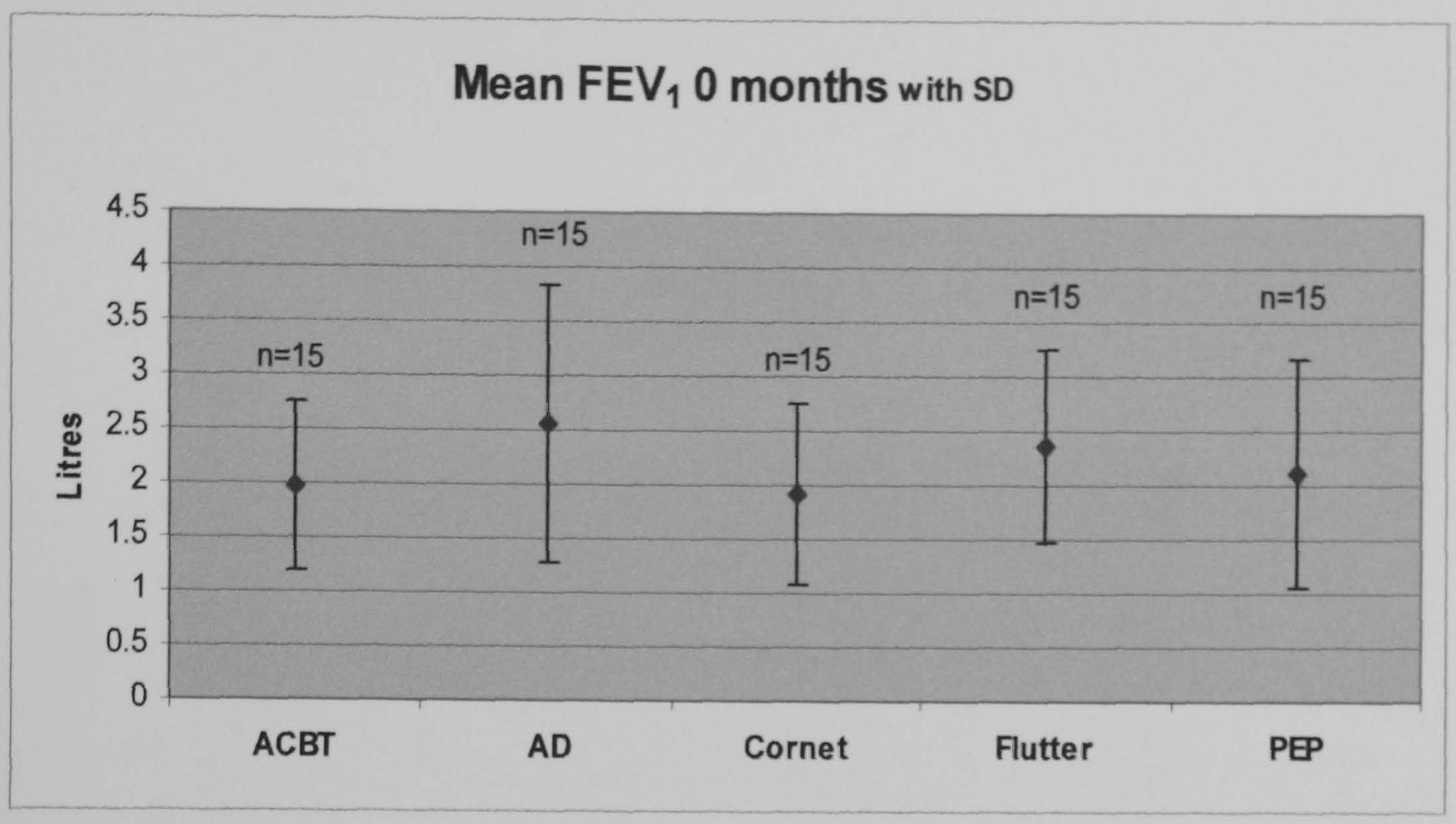
Table 6.2: Forced expiratory volume in one second (FEV_1) in litres and FEV_1 as percent predicted FEV_1, for each subject, by regimen, on entry to the study.

The individual values of FEV_1 for the 65 subjects at 0 months and 12 months, are given in Appendix 18.

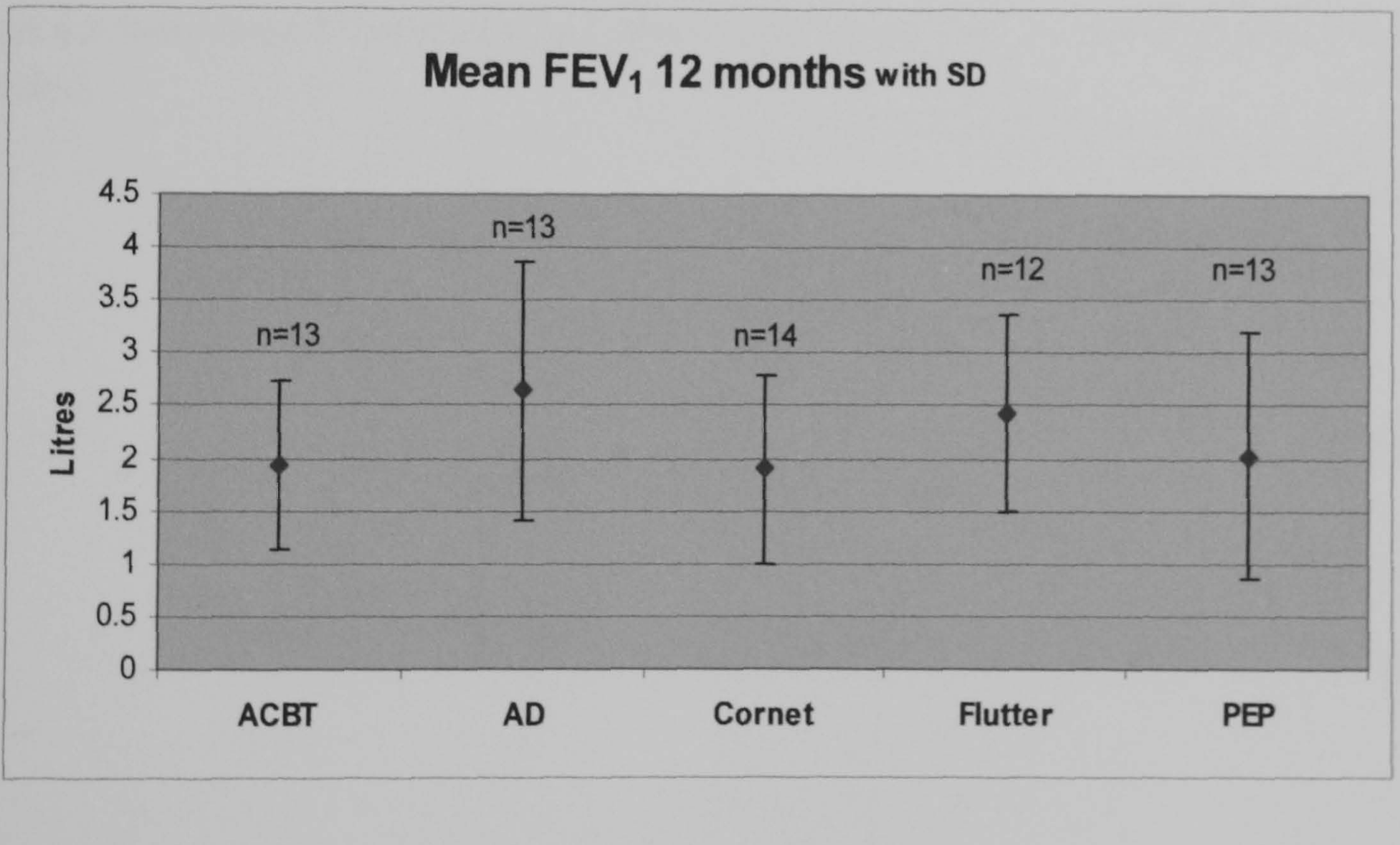
The distribution of the data was examined for forced expiratory volume in one second (FEV_1), age and body mass index (BMI). Body mass index was normally distributed and both age and FEV_1 were slightly skewed, FEV_1 owing to the outlier of one subject of 63 years of age (Appendix 19). The standard deviations were small in comparison with the mean values and after looking at both mean and median values it was considered appropriate to use the mean values for the main analysis of the data.

The primary outcome measure of forced expiratory volume in one second (FEV_1) was explored initially using intention to treat and one-way analysis of variance. It appeared that there were five random groups at baseline (0 months) $p=0.31$. Twelve months later the groups were slightly more disparate, but there were no statistically significant differences among them ($p=0.25$) (Appendix 20). The Z-scores at 0 months and at 12 months had the same p-values.

Using the mixed model analysis of variance there were no differences among the five groups (p=0.35) (Figure 6.2a and 6.2b).



a.



b.

Figure 6.2: Forced expiratory volume in one second (FEV_1): (a) 0 months (b) 12 months (bars represent standard deviation) and n = number of subjects.

Overall there was a significant deterioration in forced expiratory volume (FEV_1) in one second over time (p=0.02) (Figure 6.3).

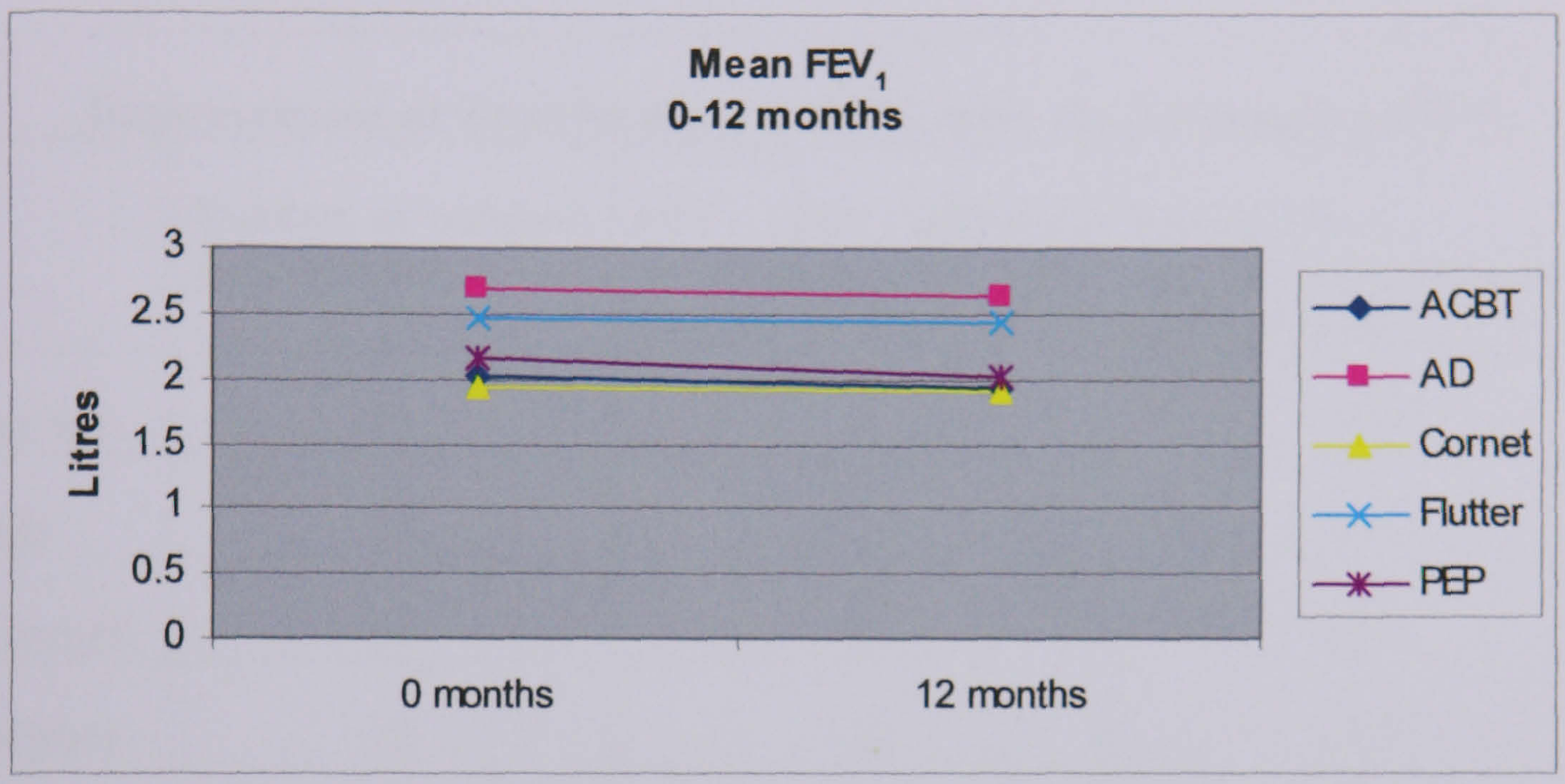


Figure 6.3: Deterioration in forced expiratory volume in one second (FEV_1) for each of the five regimens over time.

For just over half (58.5%) of the subjects there was deterioration in FEV_1 over the 12-month period. For 41.5% of the subjects, their FEV_1 either remained the same or improved (Table 6.3).

Improvement or deterioration in FEV_1 over the 12-month period			
	Number of subjects at 12 months	FEV_1 either improved or remained the same (number of subjects)	Percentage, in individual regimen, with no deterioration in FEV_1
ACBT	13	5	38.5
AD	13	7	53.9
Cornet	14	4	28.6
Flutter	12	8	66.7
PEP	13	3	32.1
	100%	41.5%	

Table 6.3: Improvement or deterioration in forced expiratory volume in one second (FEV_1) over the 12-month period.

Owing to concerns regarding possible deterioration in lung function at six months, lung function results were closely monitored (Appendix 21).

The forced expiratory volume in one second (FEV_1) as a percent of the predicted FEV_1 for the five groups is shown in Table 6.4.

FEV_1 as percent predicted FEV_1			
	0 months	**12 months**	**Percent change over 12 months**
ACBT	53.4(n=13)	51.4 (n=13)	- 2.1
AD	67.3 (n=13)	66.7 (n=13)	- 0.6
Cornet	53.9 (n=14)	52.3 (n=14)	-1.6
Flutter	66.6 (n=12)	66.1 (n=12)	- 0.4
PEP	57.6 (n=13)	53.5 (n=13)	-4.1
		Mean for the group using intention to treat	-1.76

Table 6.4: Forced expiratory volume in one second (FEV_1) as percent predicted FEV_1.

For FEV_1 as a percent of predicted FEV_1 using the mixed model analysis of variance there were no significant differences among the five groups (p=0.35). Overall there was a significant deterioration over time (p=0.02) (Figure 6.4).

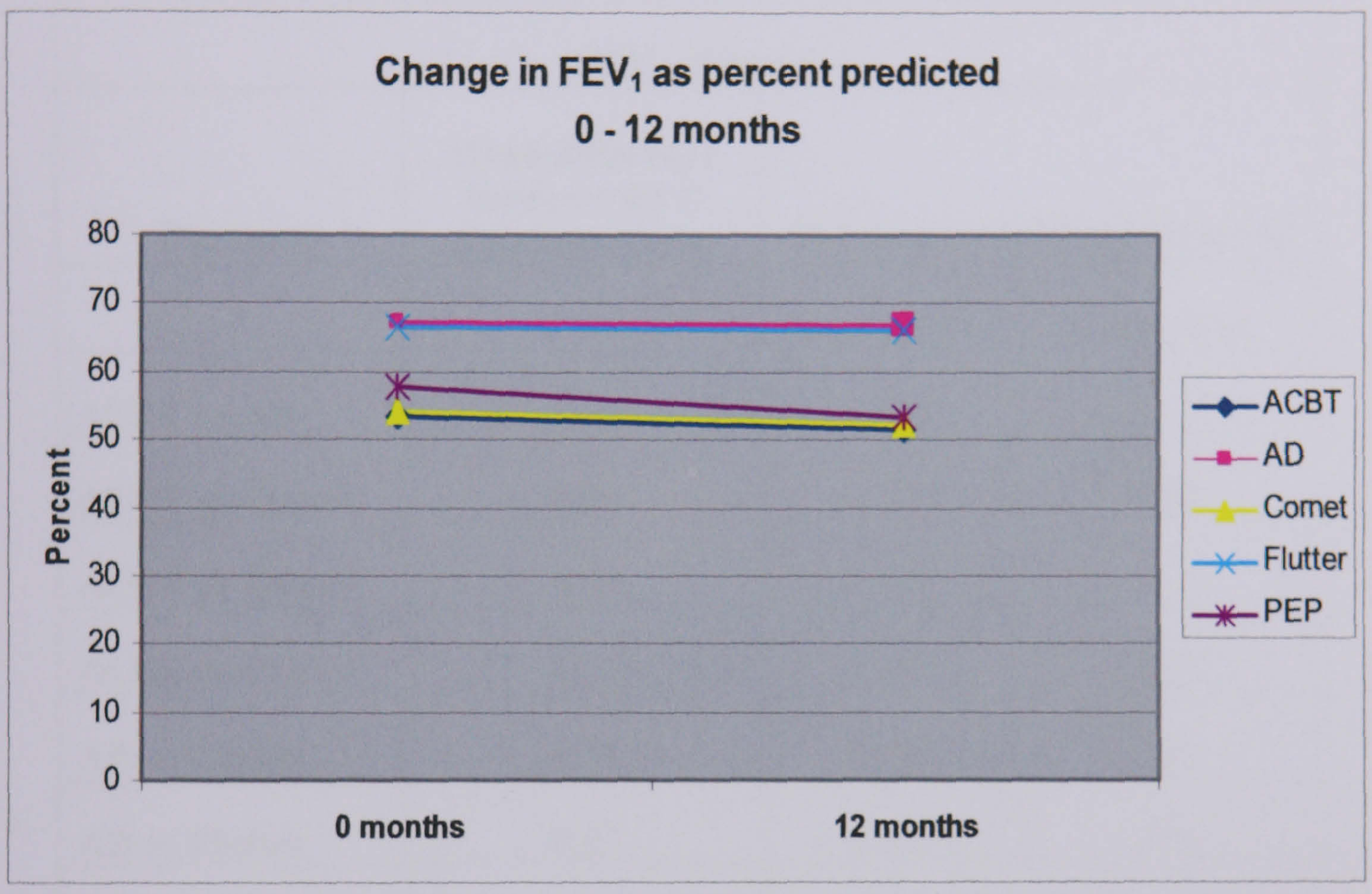


Figure 6.4: Change in forced expiratory volume in one second (FEV_1) as percent predicted FEV_1 for each of the five regimens over time.

The individual patient's change in FEV_1, as a percent of predicted FEV_1, for each regimen is presented in Appendix 22.

For the forced expiratory volume in one second (FEV_1) each group was compared with every other group and there were no statistically significant differences (Table 6.5). Each confidence interval includes zero which means that the mean difference between the groups is zero.

FEV_1 (litres)			
Regimen	**Mean difference between the 2 regimens (litres)**	**95 percent confidence interval**	
		Lower limit	Upper limit
ACBT vs AD	-0.69	-1.49	0.11
ACBT vs Cornet	0.06	-0.72	0.85
ACBT vs Flutter	-0.47	-1.28	0.35
ACBT vs PEP	-0.12	-0.92	0.68
AD vs Cornet	0.75	-0.03	1.53
AD vs Flutter	0.22	-0.60	1.03
AD vs PEP	0.57	-0.23	1.36
Cornet vs Flutter	-0.53	-1.33	0.27
Cornet vs PEP	-0.18	-0.97	0.60
Flutter vs PEP	0.35	-0.47	1.16

Table 6.5: Mean differences between each of the regimens and the 95 percent confidence intervals.

There was concern that there may have been a bias owing to sex as there were more men than women in the study. When FEV_1 was adjusted for sex using the mixed model analysis of variance there were no differences among the five treatment groups ($p=0.31$). Overall there was a deterioration over time ($p=0.02$). When adjusted for sex using FEV_1 as a percent of predicted FEV_1, again sex was not a significant predictor.

There were no differences among the five treatment arms (p=0.35) and overall there was a deterioration over time (p=0.02).

The secondary measures of forced vital capacity (FVC), maximal expiratory flow at 25 percent of forced vital capacity (MEF_{25}) and residual volume as a percent of total lung capacity (RV%/TLC) were also explored using intention to treat and n = 65.

Figure 6.5 and Table 6.6 demonstrate the changes in forced vital capacity (FVC) for the five groups over time (0 months and 12 months). Using the mixed model analysis of variance there were no significant differences in FVC among the five groups (p=0.54). Overall there was no significant change in FVC over time (p=0.14).

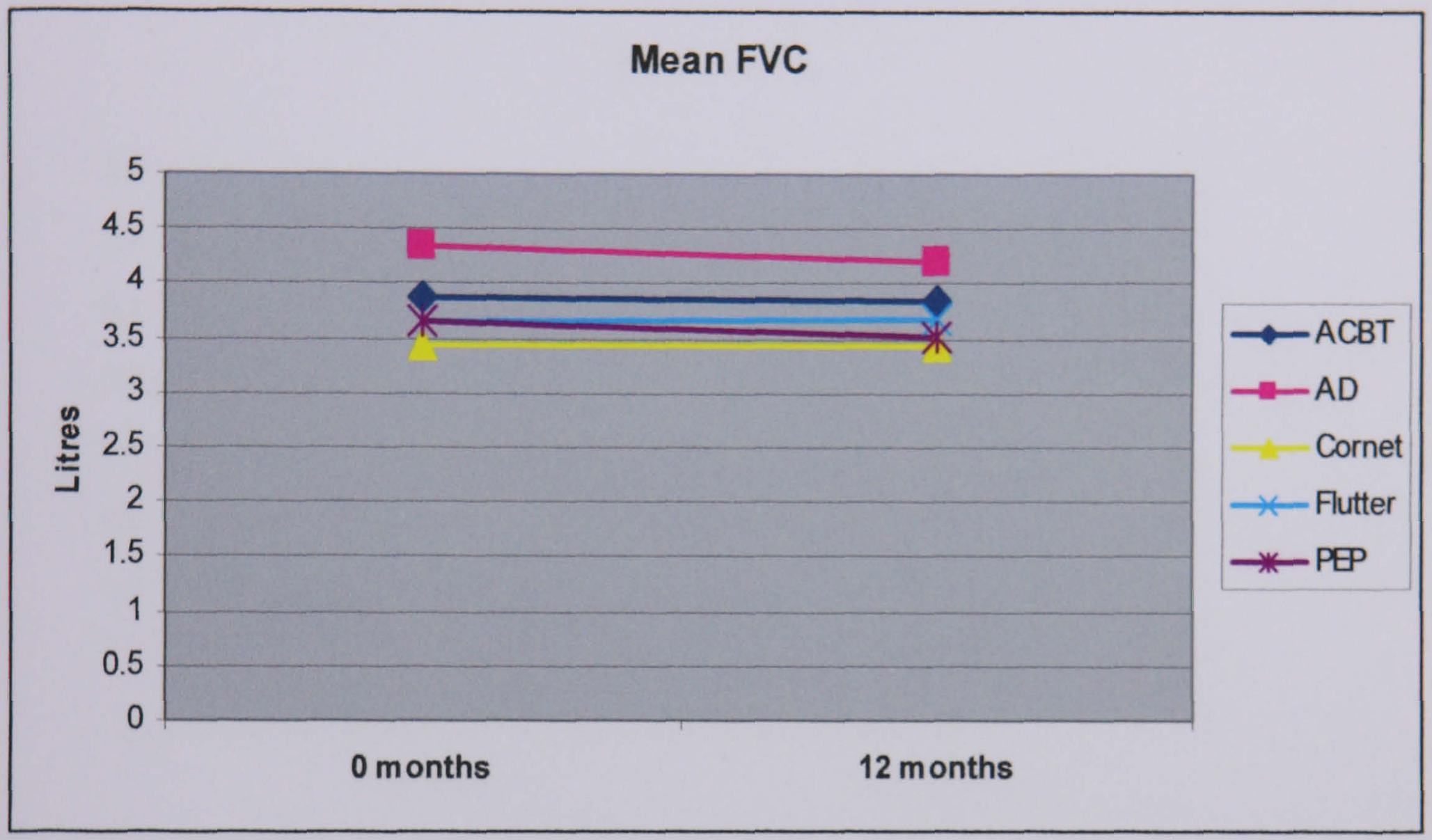


Figure 6.5: Mean forced vital capacity (FVC) for each of the five regimens over time.

Mean FVC in litres (±SD)		
	0 months	**12 months**
ACBT (n=10)	3.9 (1.3)	3.8 (1.3)
AD (n=9)	4.3 (1.1)	4.2 (1.2)
Cornet (n=11)	3.4 (1.1)	3.4 (1.2)
Flutter (n=12)	3.7 (1.1)	3.7 (0.9)
PEP (n=11)	3.7 (1.1)	3.5 (1.2)

Table 6.6: Mean forced vital capacity (FVC) in litres (± SD) for each of the regimens.

Figure 6.6 and Table 6.7 demonstrate the changes for maximal expiratory flow at 25% of forced vital capacity (MEF_{25}) for the five groups over time (0 months and 12 months). Using the mixed model analysis of variance there were no significant differences in MEF_{25} among the five groups (p=0.54). Overall there was no significant change in MEF_{25} over time (p=0.14).

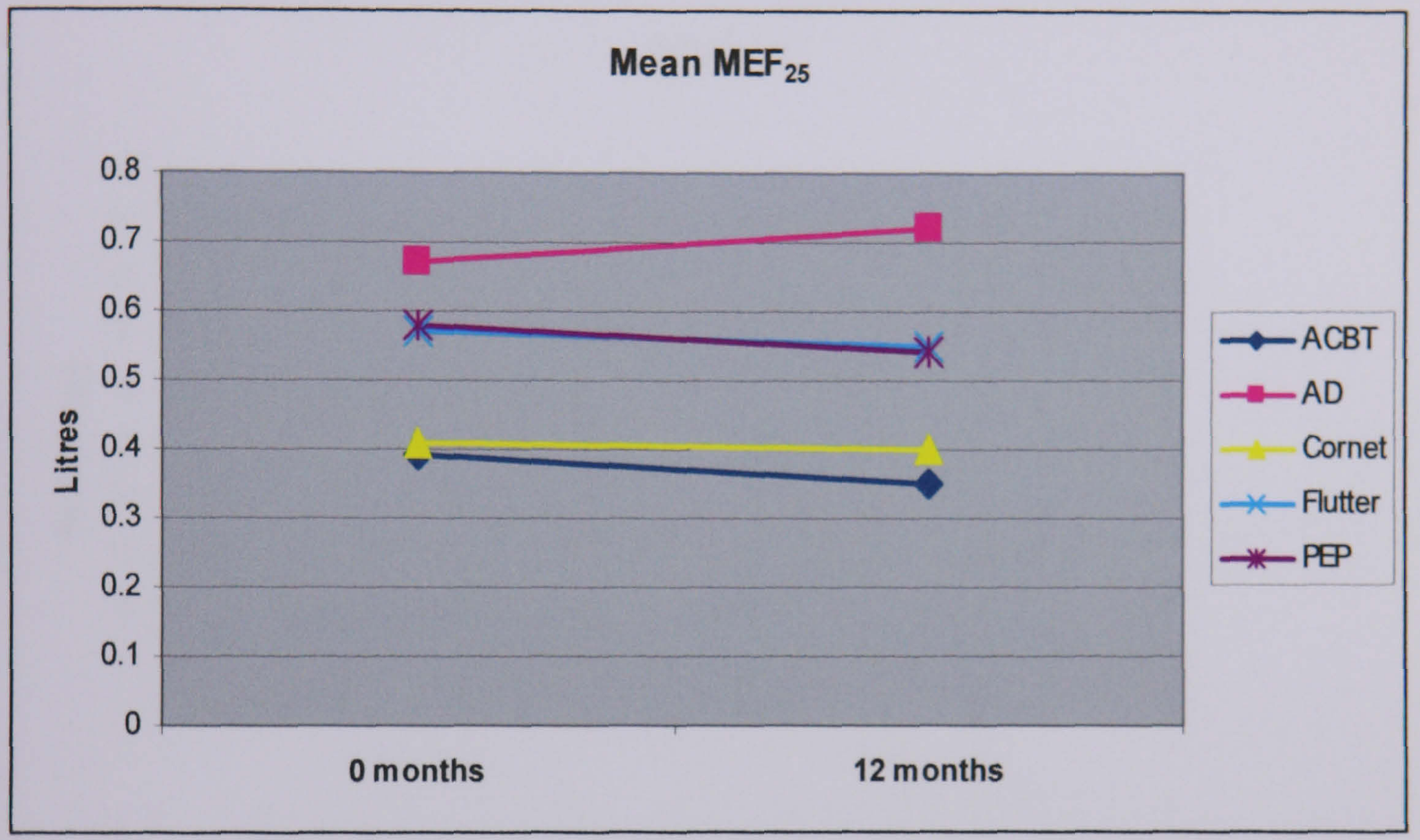


Figure 6.6: Mean maximal expiratory flow at 25 percent of forced vital capacity (MEF_{25}) for each of the five regimens over time.

Mean MEF_{25} in litres (± SD)		
	0 months	**12 months**
ACBT (n=10)	0.39 (0.25)	0.35 (0.20)
AD (n=9)	0.67 (0.41)	0.72 (0.45)
Cornet (n=11)	0.41 (0.30)	0.40 (0.26)
Flutter (n=12)	0.57 (0.52)	0.55 (0.54)
PEP (n=11)	0.58 (0.57)	0.54 (0.53)

Table 6.7: Mean maximal expiratory flow at 25 percent of forced vital capacity (MEF_{25}) (± SD) for each of the regimens.

Figure 6.7 and Table 6.8 demonstrate the changes in residual volume as a percent of total lung capacity (RV%TLC) for the five groups over time (0 months and 12 months). Using the mixed model analysis of variance there were no significant differences in RV%TLC among the five groups (p=0.21). Overall there was no significant change in RV%TLC over time (p=0.24).

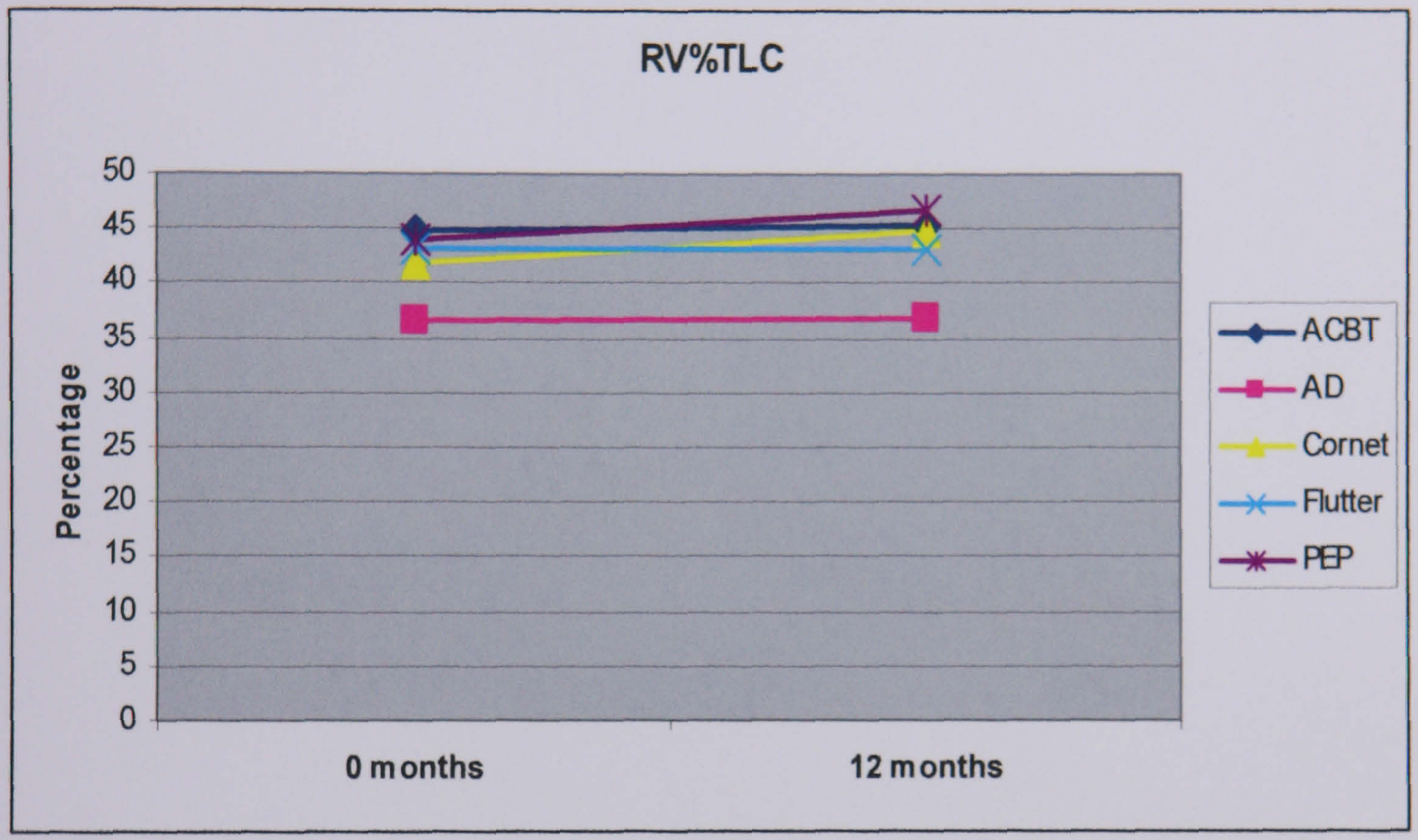


Figure 6.7: Mean residual volume as a percent of total lung capacity (RV%TLC) for each of the five regimens over time.

Mean RV%TLC (±SD)		
	0 months	**12 months**
ACBT (n=10)	44.9 (9.9)	45.3 (10.2)
AD (n=9)	36.5 (8.1)	36.9 (10.1)
Cornet (n=11)	41.7 (11.0)	44.7 (12.0)
Flutter (n=12)	43.0 (12.1)	43.2 (11.2)
PEP (n=11)	44.0 (14.4)	46.7 (16.4)

Table 6.8: Mean residual volume as a percent of total lung capacity (RV%TLC) (± SD) for each of the regimens.

The summary results, for the subjects who remained on the study, for forced expiratory volume in one second, forced vital capacity, residual volume as a percent of total lung capacity and maximal expiratory flow at 25 percent of forced vital capacity at 0 months, 6 months and 12 months are given in Appendix 21.

Body mass index

The values for body mass index (BMI) (weight in kilograms divided by the square of the height in metres), on entry to the study, are given in Table 6.9.

Body mass index (BMI) on entry to the study				
ACBT	**AD**	**Cornet**	**Flutter**	**PEP**
19.3	24.7	22.2	22.0	17.3
22.2	27.0	25.2	29.1	24.4
19.9	22.2	21.0	21.8	22.3
20.5	24.1	24.7	25.5	20.6
23.1	16.6	17.0	23.6	19.8
22.8	27.8	17.4	22.2	20.0
24.8	20.1	21.5	16.3	20.7
15.4	25.4	21.8	24.1	26.1
18.1	23.4	22.2	23.1	17.4
26.8	20.8	16.0	21.3	20.1
19.3	22.7	16.0	22.8	28.5
24.7	24.4	20.6	20.4	20.6
13.4	20.8	23.4	26.1	25.2
21.7	17.2	23.8	24.5	21.1
19.1	22.0	20.7	18.6	17.8
Mean BMI and standard deviation				
21.1 (3.0)	22.6 (3.2)	20.9 (3.0)	22.8 (3.1)	21.5 (3.3)

Table 6.9: Body mass index on entry to the study.

The data for body mass index (BMI) was normally distributed (Appendix 19). The changes in BMI over time, for the completers (n=53), are shown graphically in Figure 6.8 and summarised in Table 6.10. The groups both at 0 and 12 months fell within the ideal body weight range of 18.5 – 24.9. Using the mixed model analysis of variance there were no significant differences in BMI among the five groups (p=0.36). Overall there was no significant change in BMI over time (p=0.94).

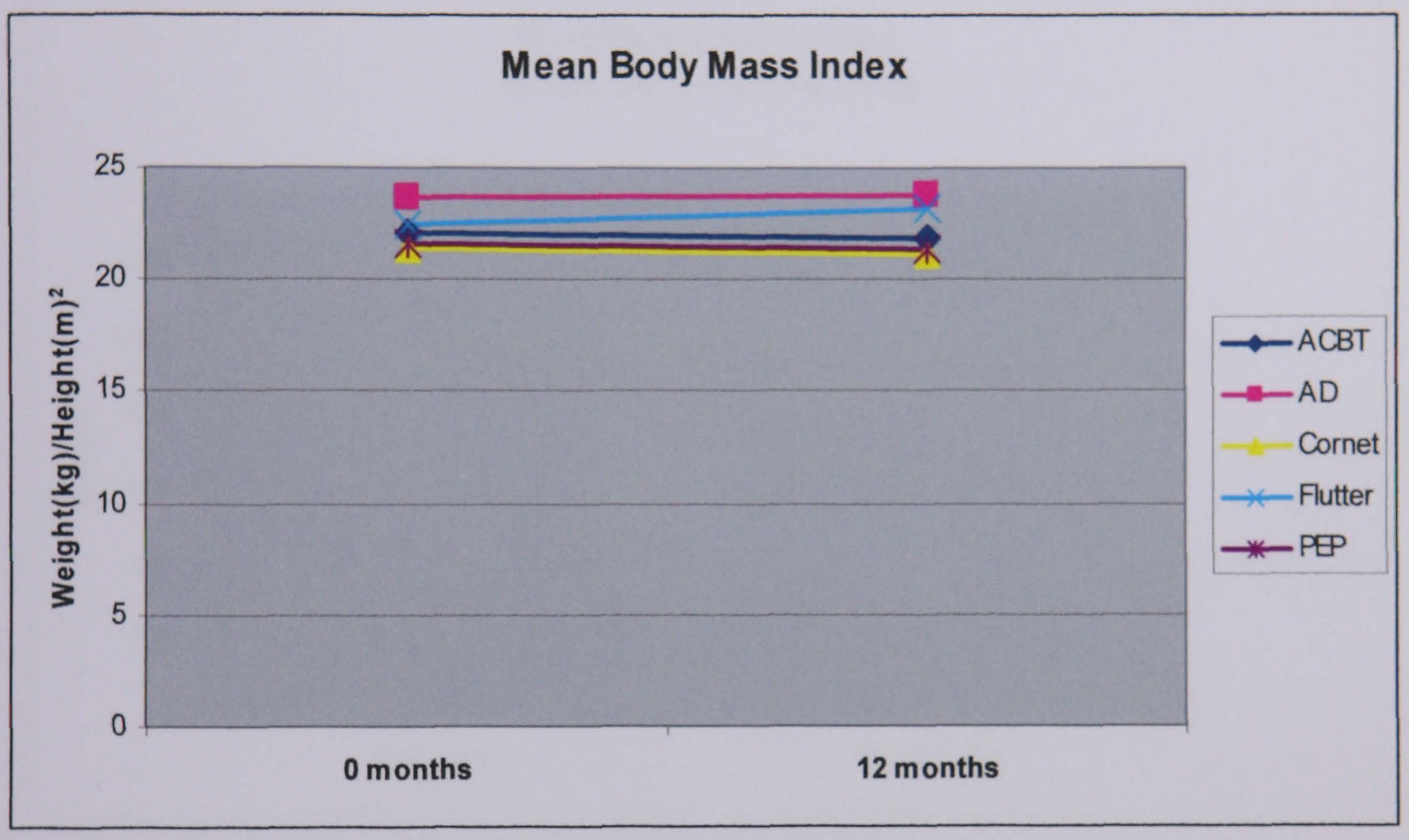


Figure 6.8: Mean body mass index (BMI) for each of the five regimens over time.

Mean Body Mass Index in Weight(kg)/Height(m)^2 (± SD)		
	0 months	**12 months**
ACBT (n=10)	22.1 (2.7)	21.8 (3.4)
AD (n=9)	23.7 (2.7)	23.8 (2.7)
Cornet (n=11)	21.3 (2.6)	21.1 (2.8)
Flutter (n=12)	22.5 (3.3)	23.2 (3.3)
PEP (n=11)	21.6 (3.8)	21.4 (3.7)

Table 6.10: Mean body mass index (BMI) (± SD) for each of the regimens.

Exercise capacity

The distance covered by the subjects, in metres, on entering the study at 0 months and on completion of the study at 12 months is shown in Figure 6.9 and Table 6.11. Using the mixed model analysis of variance there were no significant differences among the five groups (p=0.52). Overall there was no significant change in distance over time (p=0.57).



Figure 6.9: Mean distance modified shuttle test for the five regimens over time.

Modified Shuttle Test Mean distance in metres (± SD)		
	0 months	**12 months**
ACBT (n=7)	1204 (238)	1161 (268)
AD (n=6)	1072 (306)	1130 (342)
Cornet (n=10)	978 (242)	982 (296)
Flutter (n=12)	1083 (298)	1137 (307)
PEP (n=11)	961 (342)	939 (393)

Table 6.11: Distance covered during the modified shuttle test.

Not all subjects who completed the study were available for the modified shuttle test at 12 months (Table 6.12).

Number completing the Modified Shuttle Test (number available in parentheses)		
	0 months	**12 months**
ACBT	13 (15)	7 (10)
AD	12 (15)	6 (9)
Cornet	15 (15)	10 (11)
Flutter	14 (15)	12 (12)
PEP	14 (15)	11 (11)

Table 6.12: Number of subjects completing the modified shuttle test.

Reasons for not undertaking the modified shuttle test included musculoskeletal injuries (knee and ankle), cardiomyopathy, influenza, acute exacerbation of infection, exhaustion (after a night out!), lack of time within the annual review schedule, inappropriate footwear and following a motor vehicle accident.

There were no statistically significant differences, among the groups, in the distance covered during the modified shuttle test, but there were clinically important differences (the minimally important difference, that is increases of > 40 metres) (Bradley *et al* 2000) in the modified shuttle distance when 0 months was compared with 12 months, but only in the autogenic drainage and flutter regimens (Table 6.13).

Minimally important difference (MID) for the Modified Shuttle Test (> 40metres)			
	Distance at 0 months (metres)	**Distance at 12 months** (metres)	**Difference** (metres)
AD (n=6)	1072	1130	58
Flutter (n=12)	1083	1137	54

Table 6.13: Minimally important difference for the modified shuttle test.

The reasons for stopping the modified shuttle test included completing the test, breathlessness, fatigue or both breathlessness and fatigue. Apart from those who finished the test, there was considerable intra-subject variation as to whether it was breathlessness or leg fatigue or both which caused them to stop.

Table 6.14 shows the baseline oxygen saturation levels before the modified shuttle test at 0 and 12 months, and the lowest level recorded during the shuttle test. As only two of the results were outside the ± 2% error of the pulse oximeter the data was not analysed further, but there was a trend for the level of desaturation during exercise to be less at 12 months with both AD and the cornet.

	Oxygen saturation (SpO_2) associated with the Modified Shuttle Test (± SD)			
	0 months		12 months	
	Pre-MST SpO_2	Lowest SpO_2 during MST	Pre-MST SpO_2	Lowest SpO_2 during MST
ACBT (n=7)	96.7 (1.3)	90.0 (4.2) Range: 82-95	96.4 (0.8)	89.6 (3.6) Range: 83-94
AD (n=6)	97.0 (1.8)	89.2 (4.8) Range: 83-95	97.7 (0.8)	92.7 (2.6) Range: 89-95
Cornet (n=10)	96.7 (1.2)	84.7 (7.6) Range: 75-92	96.3 (1.3)	87.5 (4.8) Range: 80-95
Flutter (n=12)	97.5 (1.7)	90.2 (5.3) Range: 82-97	96.8 (1.4)	90.4 (3.7) Range: 86-97
PEP (n=11)	96.6 (1.6)	89.0 (7.4) Range: 71-96	97.2 (1.6)	89.6 (7.4) Range: 74-96

Table 6.14: Baseline oxygen saturation (SpO_2) before starting the modified shuttle test (MST) at 0 months and 12 months, and lowest oxygen saturation recorded during the MST.

The results from the Borg - breathlessness scores and Borg - leg fatigue scores are demonstrated in Figures 6.10 and 6.11, but owing to the small numbers it would be inappropriate to analyse these any further. They demonstrate that the scores are sensitive to the increased breathlessness and fatigue of maximal exertion.

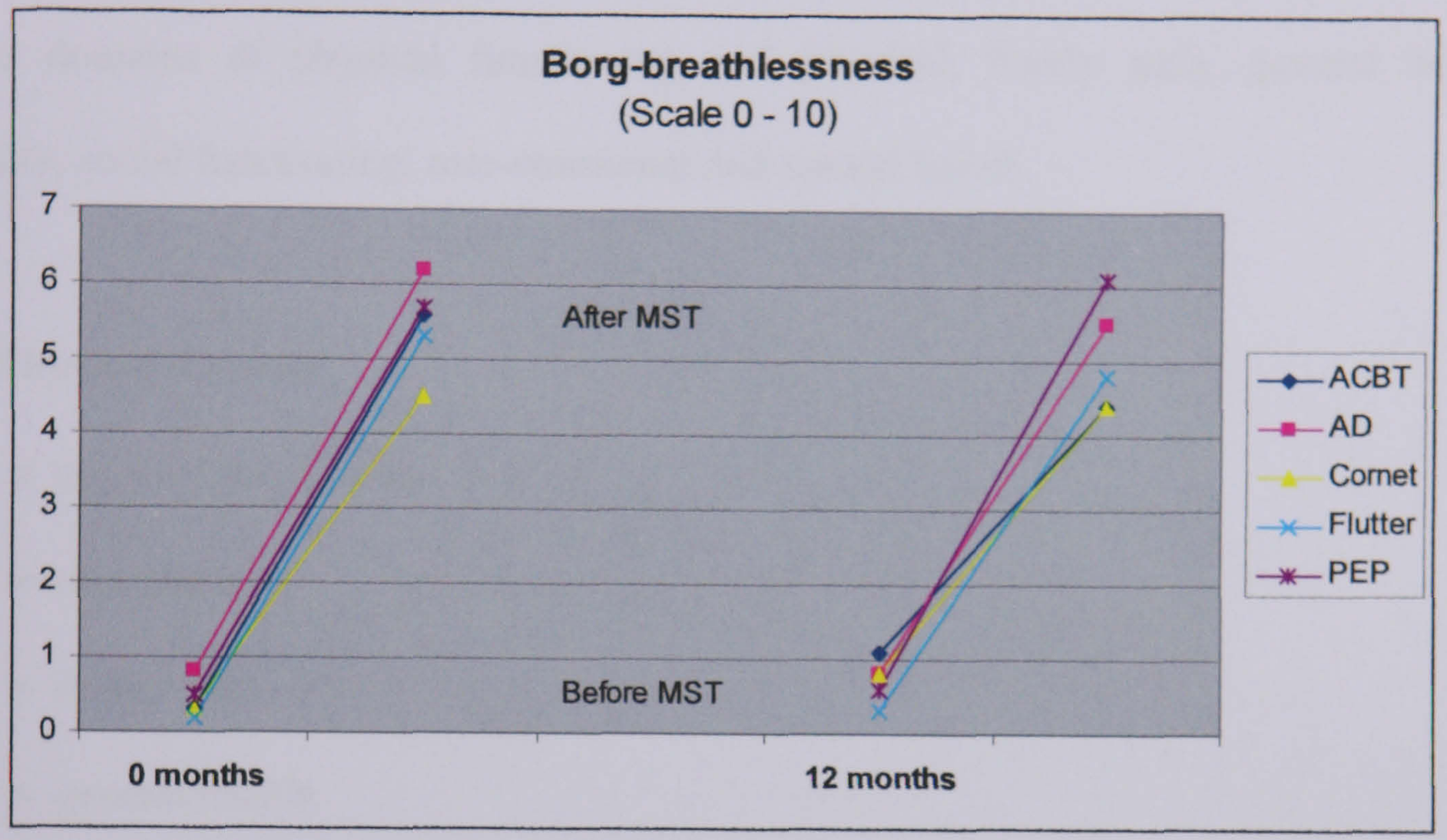


Figure 6.10: Borg scores for breathlessness before and immediately after the modified shuttle test (MST) (0 = not at all breathless, 10 = maximally breathless).

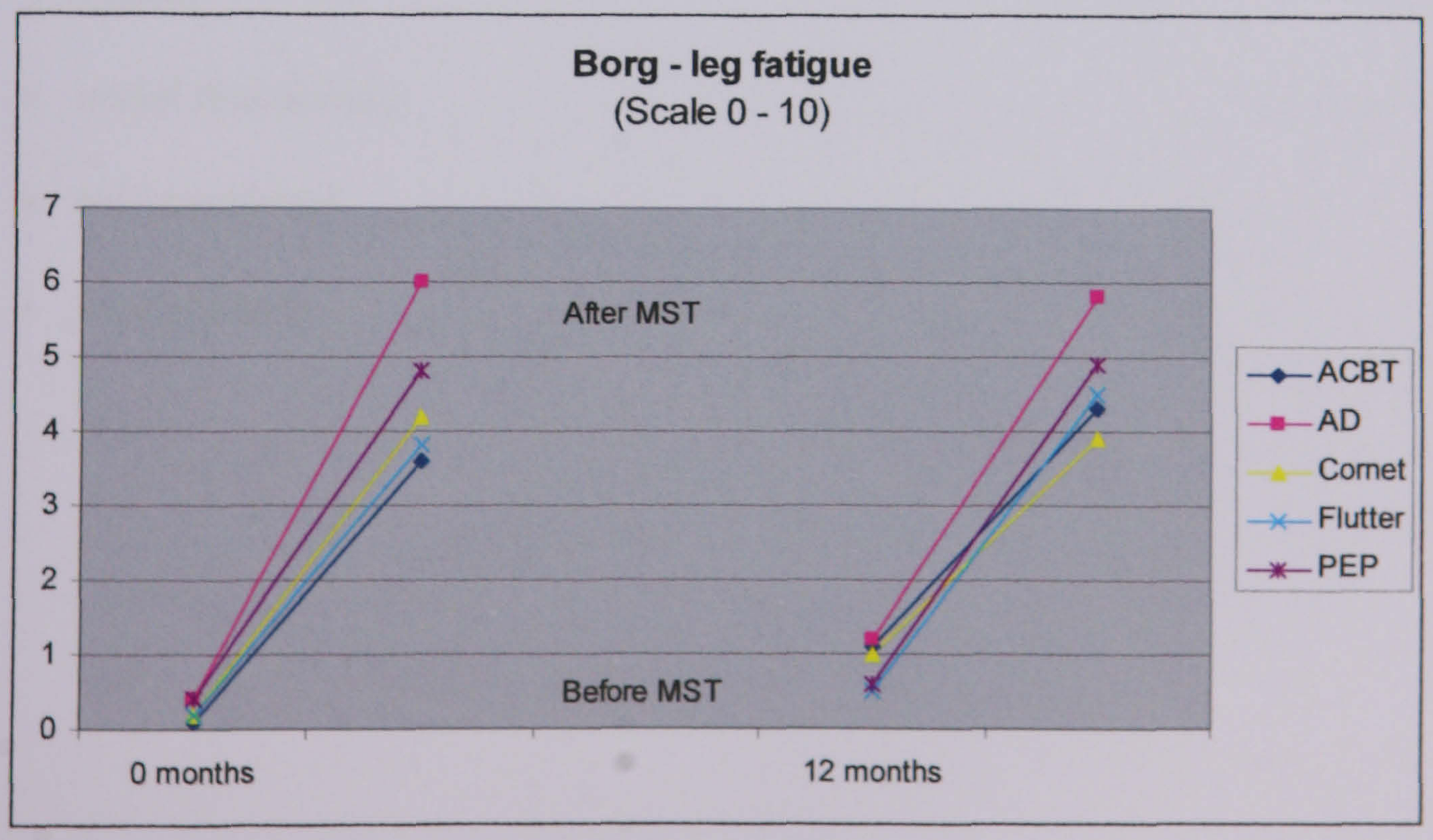


Figure 6.11: Borg scores for leg fatigue before and immediately after the modified shuttle test (MST) (0 = not at all tired, 10 = maximally tired).

Quality of life

Short Form-36 questionnaire

Owing to the small numbers in each group, it was decided to analyse the Short Form-36 questionnaire (SF-36) in the aggregated domains of physical and mental rather than the eight domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health.

Physical domain:

- physical functioning
- role-physical
- bodily pain
- general health

Mental domain:

- vitality
- social functioning
- role-emotional
- mental health.

The results of the physical domain are summarised in Figure 6.12. and Table 6.15. Using the mixed model analysis of variance there were no significant differences in the physical domain of the SF-36 among the 5 groups (p=0.99). Overall there was a trend towards a deterioration over time (p=0.05).

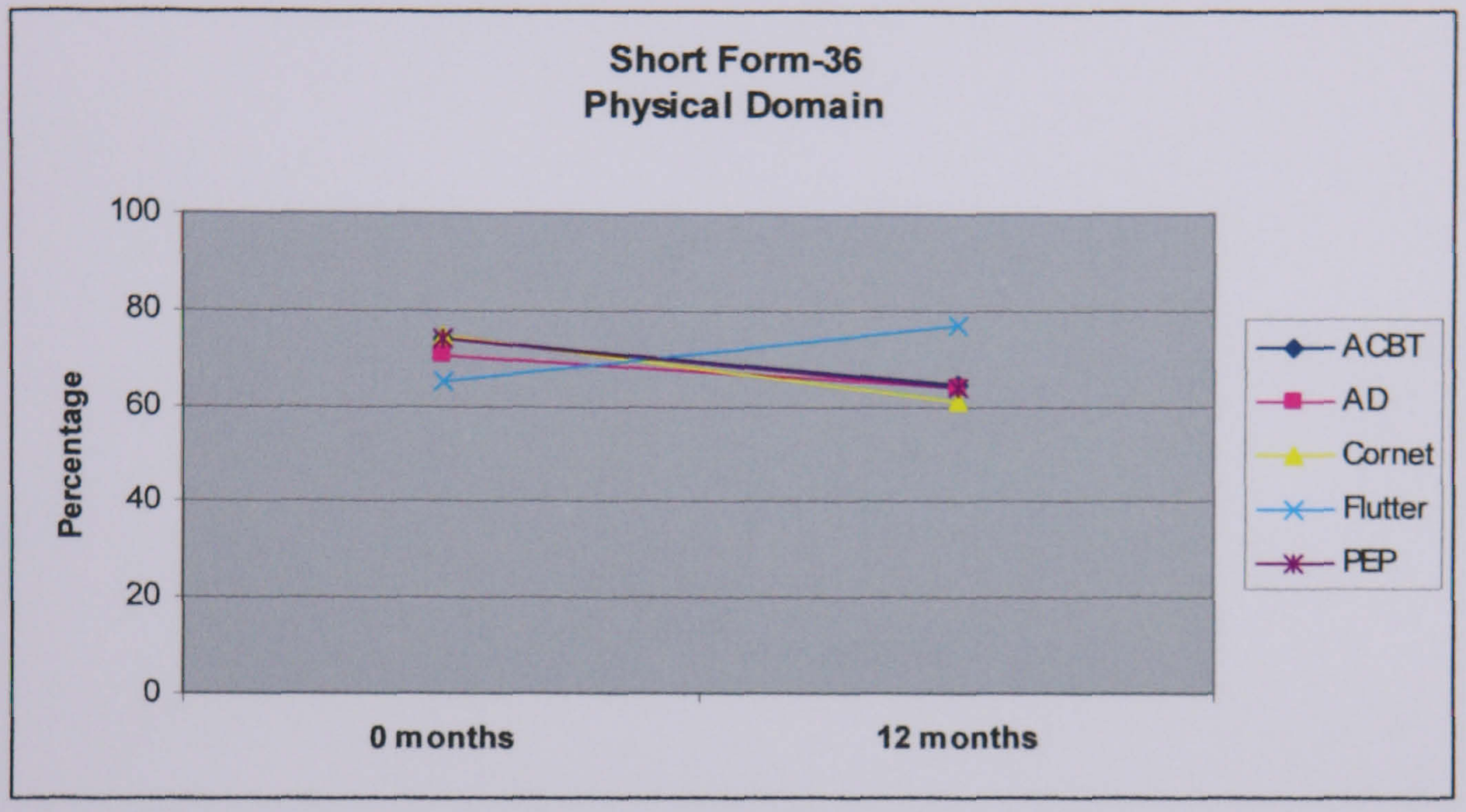


Figure 6.12: Short Form-36 physical domain for each of the five regimens over time.

Short Form-36 Physical Domain (± SD)		
	0 months	**12 months**
ACBT (n=10)	74.1 (28.4)	64.5 (33.4)
AD (n=8)	70.7 (33.1)	63.9 (36.0)
Cornet (n=9)	74.3 (31.4)	61.2 (33.6)
Flutter (n=12)	65.0 (29.6)	76.9 (25.1)
PEP (n=11)	73.7 (27.3)	64.1 (32.2)

Table 6.15 Short Form-36 physical domain (percent).

The results of the mental domain of the SF-36 are summarised in Figure 6.13 and Table 6.16. Using the mixed model analysis of variance there were no significant differences in the mental domain of the SF-36 among the 5 groups (p=0.27). Overall there was a significant deterioration over time (p=0.002).

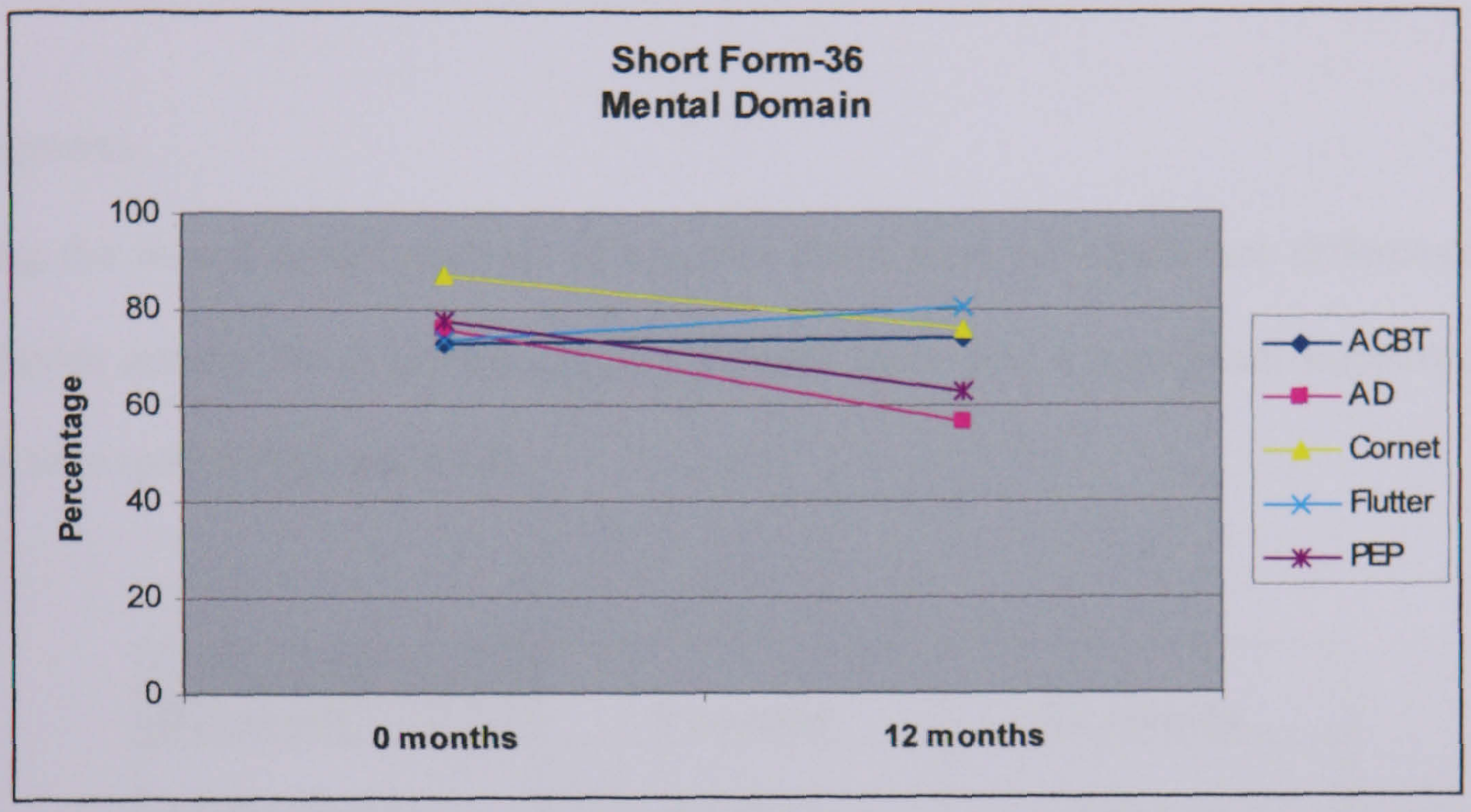


Figure 6.13: Short Form-36 mental domain for each of the five regimens over time.

Short Form-36 Mental Domain (± SD)		
	0 months	**12 months**
ACBT (n=10)	73.2 (27.2)	74.2 (30.6)
AD (n=8)	75.8 (24.0)	56.2 (29.9)
Cornet (n=9)	87.3 (15.7)	75.7 (24.1)
Flutter (n=12)	73.6 (24.3)	80.3 (24.9)
PEP (n=11)	77.5 (20.9)	63.2 (31.2)

Table 6.16: Short Form-36 mental domain (percent).

Chronic Respiratory Questionnaire

The four domains of dyspnoea, fatigue, emotion and mastery. of the chronic respiratory questionnaire (CRQ), were analysed.

Dyspnoea

Using the mixed model analysis of variance there were no significant differences in dyspnoea among the 5 groups (p=0.7). Overall there was a significant improvement over time (p=0.01) (Table 6.17).

Dyspnoea	**0 months**	**12 months**
ACBT (n=10)	4.1 (1.1)	4.8 (1.1)
AD (n=8)	4.2 (0.4)	4.7 (1.2)
Cornet (n=10)	4.5 (0.9)	4.8 (1.4)
Flutter (n=12)	3.9 (1.3)	5.2 (1.0)
PEP (n=11)	3.7 (0.6)	4.6 (1.3)

Table 6.17: Chronic Respiratory Questionnaire – Dyspnoea.

Fatigue

Using the mixed model analysis of variance there were no significant differences in fatigue among the 5 groups (p=0.85). Overall there was no significant difference over time (p=0.69) (Table 6.18).

Fatigue	**0 months**	**12 months**
ACBT (n=10)	4.6 (1.3)	4.9 (1.7)
AD (n=8)	4.0 (1.6)	4.2 (1.5)
Cornet (n=10)	5.1 (1.2)	4.4 (1.5)
Flutter (n=12)	4.4 (1.4)	4.7 (1.7)
PEP (n=11)	4.8 (0.8)	4.4 (1.4)

Table 6.18: Chronic Respiratory Questionnaire – Fatigue.

Emotion

Using the mixed model analysis of variance there were no significant differences in emotion among the 5 groups (p=0.39). Overall there was no significant difference over time (p=0.44) (Table 6.19).

Emotion	**0 months**	**12 months**
ACBT (n=10)	5.3 (0.9)	5.2 (1.5)
AD (n=8)	4.4 (1.4)	4.8 (0.8)
Cornet (n=10)	5.8 (0.6)	5.3 (1.3)
Flutter (n=12)	5.3 (1.2)	5.2 (1.4)
PEP (n=11)	5.3 (0.9)	5.0 (1.2)

Table 6.19: Chronic Respiratory Questionnaire – Emotion.

Mastery

Using the mixed model analysis of variance there were no significant differences in mastery among the 5 groups (p=0.82). Overall there was no significant difference over time (p=0.37) (Table 6.20).

Mastery	**0 months**	**12 months**
ACBT (n=10)	6.3 (0.8)	6.1 (1.2)
AD (n=8)	5.7 (1.4)	5.8 (1.5)
Cornet (n=10)	6.4 (0.7)	5.9 (1.2)
Flutter (n=12)	6.0 (1.1)	6.0 (1.0)
PEP (n=11)	6.3 (0.6)	6.2 (0.8)

Table 6.20: Chronic Respiratory Questionnaire – Mastery.

Minimally important difference in the chronic respiratory questionnaire

There were minimally important improvements in dyspnoea in four of the five groups at 12 months. From Redelmeier *et* al (1996) a change of 0.5 is said to represent a small difference in symptoms, 1.0 a moderate difference and 1.5 a large difference (Table 6.21).

Minimally important difference (MID)		
Dyspsnoea		
ACBT	0 – 12 months	Small improvement (0.7)
AD	0 – 12 months	Small improvement (0.5)
Flutter	0 – 12 months	Moderate improvement (1.3)
PEP	0 – 12 months	Small improvement (0.8)

Table 6.21: Minimally important differences in the Chronic Respiratory Questionnaire.

Time for treatment

The mean time for treatment varied among the regimens (Figure 6.14):

- Active cycle of breathing techniques: 19 minutes
- Autogenic drainage: 30 minutes
- Cornet: 18 minutes
- Flutter: 13 minutes
- Positive expiratory pressure mask: 16 minutes.

Using the two-sample test for equality of proportions with continuity corrections there was a significant difference in the mean time for a treatment session between the 13 minutes of the flutter and 30 minutes of autogenic drainage (p=0.036).

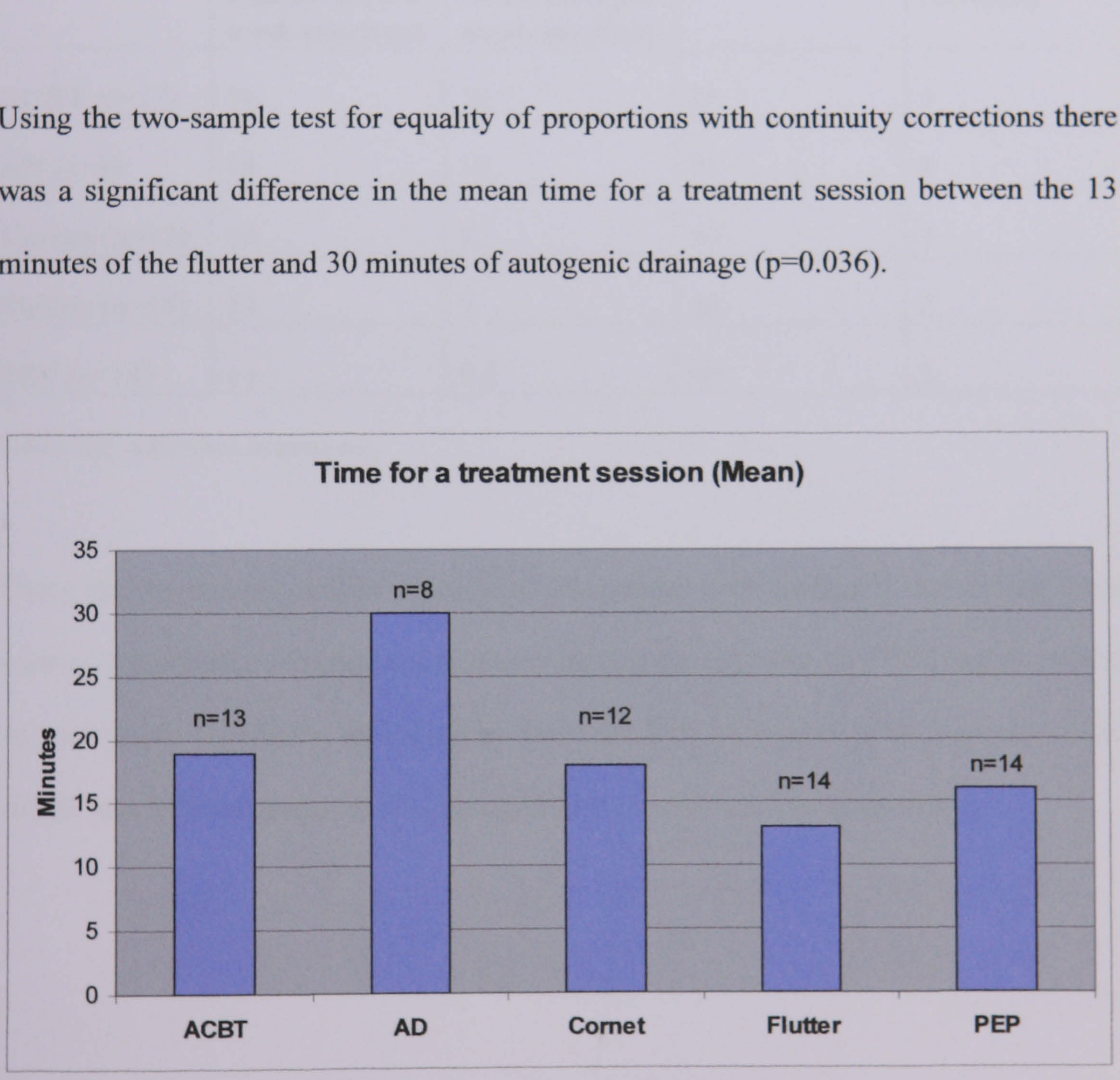


Figure 6.14: Mean time for treatment in minutes (n = number of subjects who filled in diary cards).

Adherence to treatment

Adherence to treatment was calculated using the data from the diary cards Table 6.22.

	Predicted number of treatments per week (median)	**Actual number of treatments per week (median)**	**Actual versus predicted (%)**	**Exercise days per week (median)**
ACBT (n=13)	14	12	86	3
AD (n=8)	14	10	71	4
Cornet (n=12)	14	7	50	3
Flutter (n=14)	14	7	50	2
PEP (n=14)	14	9.5	68	2

Table 6.22: Adherence to treatment.

Using the two-sample test for equality of proportions with continuity corrections there were no statistically significant differences among the regimens ($p=0.22$) and there was no statistically significant difference between the 86% adherence to the regimen of the ACBT and 50% adherence to the regimens of the cornet and flutter ($p=0.09$).

Intravenous antibiotics

Some patients in each of the regimens required intravenous antibiotics during the 12-month period. The antibiotic usage is outlined in Table 6.23. The median number of courses ranged from 1.0 to 1.5. Owing to the small numbers and the scattered nature of the data, it was not appropriate to analyse it statistically.

Courses of Intravenous Antibiotics during study period							
		Number of courses					
	Number of subjects	1	2	3	4	5	Median
ACBT	3 subjects	2	1				1
AD	5 subjects	3	1			1	1
Cornet	6 subjects	3	2	1			1
Flutter	6 subjects	4	2				1
PEP	6 subjects	3	1	2			1.5

Table 6.23: Use of intravenous antibiotics.

Lung function and exercise

From individual subjects' results of change in percent predicted forced expiratory volume in one second (FEV_1) (Appendix 22), it can be seen that there was potential for improvement in several of the fitter subjects (FEV_1 > 80% predicted) and examples of this, from each regimen, are given in Table 6.24. The five subjects improved their FEV_1 as a percent predicted (range 0.9 – 18.2%) and where possible (if not already at the

maximum distance of 1500 metres) their shuttle distance (range 70 – 130 metres which is in excess of the minimally important distance (MID) of > 40 metres [4 shuttles]). Each subject had combined exercise with an airway clearance regimen.

	Improvements in FEV_1 as percent predicted FEV_1 (single subjects)		**Percent change FEV_1** (0-12 months)	**Modified Shuttle Test Distance (metres)**		**Increase in Distance** (MID > 40 metres)
	0 months	**12 months**		**0 months**	**12 months**	
ACBT (m)	80.5	85.1	4.6	1500	1500	Maximum Distance
AD (m)	86.0	104.2	18.2	1500	1500	Maximum Distance
Cornet (m)	84.9	88.7	3.8	1420	1500	80
Flutter (f)	119.6	120.5	0.9	1080	1210	130
PEP (m)	87.5	90.4	2.9	1150	1220	70

Table 6.24: Examples of improvements, in individual subjects, in forced expiratory volume in one second (FEV_1) as percent predicted FEV_1 and exercise capacity (distance of the modified shuttle test).
(m = male, f = female, MID = minimally important difference).

Figure 6.15 represents the values for FEV_1 and FVC for a national football referee who had two periods of time when he was unable to referee. The arrows demonstrate the deterioration in his lung function when he was undertaking only his airway clearance regimen of the flutter owing, firstly to abdominal discomfort and secondly to an ankle injury.

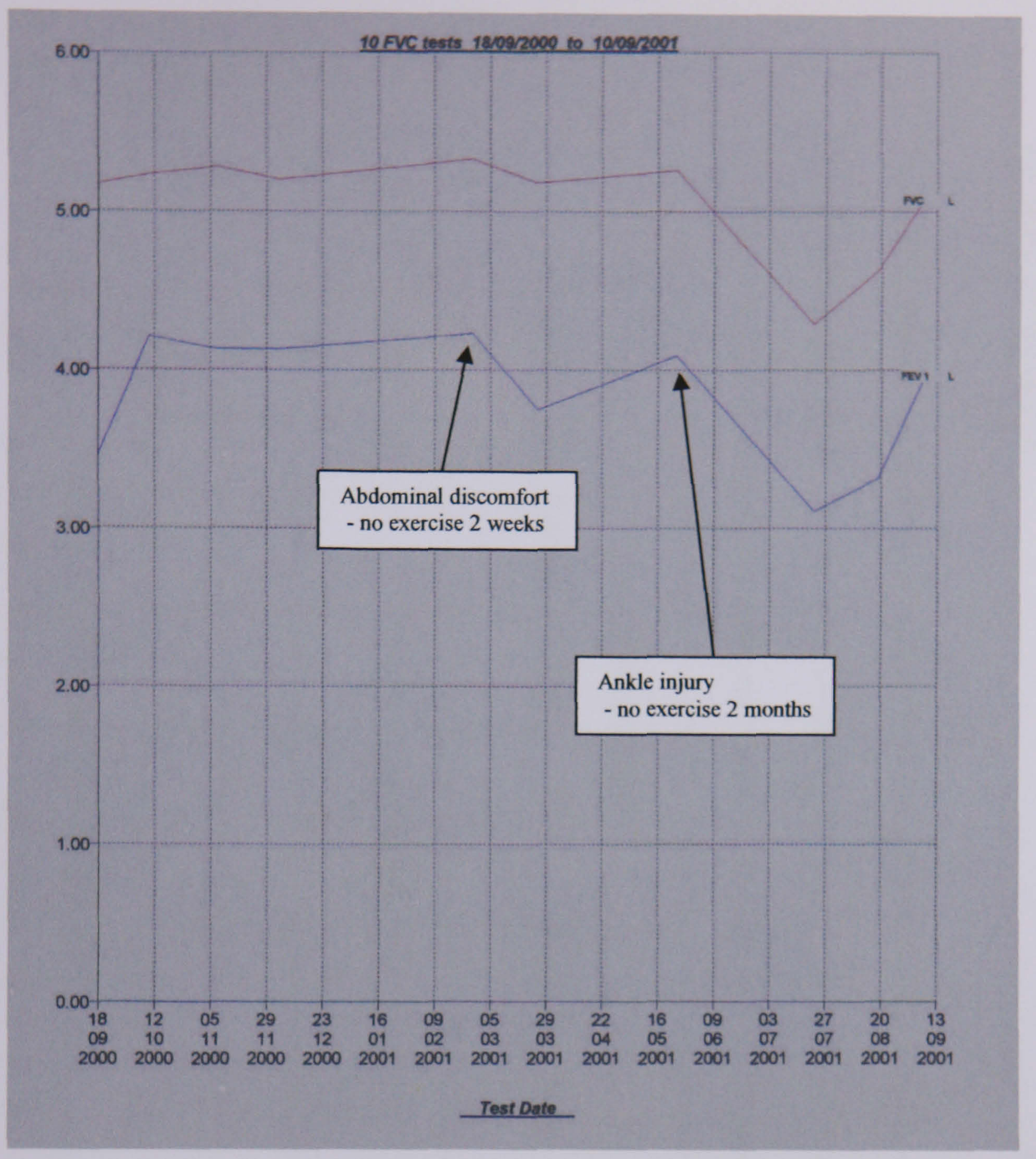


Figure 6.15: Effects of physical inactivity on lung function. The upper red line represents forced vital capacity (FVC) and the lower blue line, forced expiratory volume in one second (FEV_1).

At the lower end of the lung function scale, subjects with a forced expiratory volume in one second (FEV_1) below 50 percent predicted, both increases and decreases, in FEV_1, were documented (Appendix 22).

Patient preference

Table 6.25 details the treatment regimens of the subjects before entering the study and indicates their choice of regimen following or on discontinuing the study. At the end of the study period, or on withdrawal from the study, subjects were free to choose their airway clearance regimen. Owing to the scattered nature of the data it was not analysed statistically.

Before Study							Study Regimen	After Study				
ACBT	**AD**	**Cornet**	**Flutter**	**PEP**	**Exercise**	**None**		**ACBT**	**AD**	**Cornet**	**Flutter**	**PEP**
10	1			2		2	15 ACBT	13		1	1	
10	2		1	1 and TIRE		1	15 AD	4	10			1
11				2	1	1	15 Cornet	3		9	2	1
12	1					2	15 Flutter	1			14	
14					1		15 PEP	3		2	2	8
Number on each regimen before study								**Number on each regimen after study**				
57	4	0	1	5	2	6	75	24	10	12	19	10

Table 6.25: Airway clearance regimens before, during and after the study.

Chapter VII. Discussion

This has been a wonderful opportunity to undertake a single centre long term randomised controlled trial in airway clearance. The use of one centre has minimised bias owing to differences among centres in medical and physiotherapy management. In this chapter the findings of the study will be discussed, together with recent publications on airway clearance. The strengths, weaknesses, new findings and areas for future research are identified and discussed in Chapter VIII.

We had hoped to recruit 30 subjects to each group, to have the possibility of at least 16 subjects completing each regimen for 80% power and 5% level of significance. In spite of making contact with almost all of those who met the entry criteria and lived within a commutable distance of London (n=289), only 63 were available and willing to enter the study (Figure 6.1, p.163). At the time of setting up the study, it was not appreciated that so many would be unavailable and only by including some of those newly referred to Royal Brompton Hospital was it possible to have 75 subjects entering the study over a period of four years.

The assessment of the impact of physiotherapy on lung disease is difficult in long term studies as other treatment strategies of the care package are continuously under development (Doring & Hoiby 2004). It is well recognised that distinction among the airway clearance regimens has become blurred and this has led to contradiction and confusion in the literature. In this study considerable effort was taken to involve the original proponents of the regimens in order that the regimens used in the study were as described and undertaken by the proponents.

The null hypothesis

The hypothesis of the thesis was that there are no significant differences among the airway clearance regimens of the active cycle of breathing techniques, autogenic drainage, cornet, flutter and positive expiratory pressure over a period of one year. The results of this study support the null hypothesis. The primary outcome measure was forced expiratory volume in one second. There were several secondary or exploratory outcome measures. These were other measures of lung function (forced vital capacity, maximal expiratory flow at 25% of forced vital capacity and residual volume as a percent of total lung capacity), body mass index, exercise capacity, quality of life (Short Form-36 and Chronic Respiratory Questionnaire), time for treatment, adherence to treatment and courses of intravenous antibiotics.

There were no statistically significant differences, over the period of 12 months, among the regimens in the primary outcome measure of forced expiratory volume in one second ($p=0.35$). Overall there was a significant deterioration in forced expiratory volume in one second over time ($p=0.02$), but this deterioration of -1.8% (as a percent of predicted forced expiratory volume in one second) is within the international average of -2.0%.

In the secondary or exploratory outcome measures there were no statistically significant differences in the other measures of lung function, body mass index or exercise capacity. The Short Form-36 identified a significant deterioration in both the physical ($p=0.05$) and mental ($p=0.002$) domains over time, but there were no significant differences among the regimens.

The Chronic Respiratory Questionnaire identified an improvement over time in the domain of dyspnoea. This is interesting as it is the component of the questionnaire that is individualised to each subject with each subject selecting, on entry to the study, up to five activities which make him / her feel breathless. The statistical difference was reflected in the minimally important difference in all regimens except the cornet (Table 6.21, p.193). More regular airway clearance may reduce the sensation of dyspnoea without a corresponding improvement in lung function or the subjective sensation of dyspnoea may be influenced by changes in the subject's internal locus of control.

The average time for a treatment session ranged from 13 minutes for the flutter regimen to 30 minutes for autogenic drainage. The only significant difference, in time, was between the regimens of the flutter and autogenic drainage ($p<0.04$). The time taken for treatment may influence a patient's choice of regimen and adherence to treatment.

Unexpectedly, there was a trend towards increased adherence to airway clearance with the regimens of the active cycle of breathing techniques and autogenic drainage, neither of which requires a device. This was not statistically significant, but may reflect the additional burden of regular cleaning of a piece of equipment over a period of time and the need to have the equipment with you when there is an opportune moment for treatment.

Lung function

The deterioration in FEV_1 as a percent predicted FEV_1 was close to or less than the current international average of -2.0 percent in all but the positive expiratory pressure regimen. The overall average for the group was -1.8 percent.

It was important to closely monitor lung function in the patients on the study as McIlwaine *et al* (2001) in their long term study comparing the airway clearance regimens of positive expiratory pressure and flutter had identified, for those on the flutter regimen, a reduction in lung function, increased hospitalisation and increased use of antibiotics after six months. There were no concerns, with respect to lung function, regarding any of the regimens of this thesis at six months. Over 66 percent (eight out of 12 subjects) on the flutter regimen demonstrated either no change or an improvement in forced expiratory volume in one second at 12 months. The subjects in the study by McIlwaine *et al* were children with a mean age of 10.1 years (range: 6-17 years). The mean age for the subjects in this thesis was 28.7 years (range: 17-63 years). The differences in outcome between the flutter regimens may be a reflection of the different age groups, but this requires further investigation.

Females with cystic fibrosis have a steeper decline in lung function than males, and those with pancreatic insufficiency have a steeper decline than those who are pancreatic sufficient (Corey *et al* 1997). There were more men in the study of this thesis (Table 6.1, p.165), but this was reflected across all groups and when the primary outcome measure of forced expiratory volume in one second was adjusted for sex there were no differences among the regimens. Pancreatic insufficiency was similar across all groups (Appendix 16, p.258).

Exercise and airway clearance

A progressive decrease in exercise capacity is a major problem for many people with cystic fibrosis. This is probably a consequence of both deterioration in lung function leading to a decrease in ventilatory capacity and malnutrition leading to a loss in muscle

strength (de Jong *et al* 1997b). It was interesting to note that there were no statistically significant differences in the modified shuttle test, but there were increases in distance which were of clinical importance, as defined by the minimally important difference, that is an increase of > 40 metres.

De Jong *et al* (1997b) studied the relationship between dyspnoea, pulmonary function and exercise capacity in people with cystic fibrosis. There was a good correlation between pulmonary function and exercise capacity. Breathlessness, as assessed by the modified Borg scale, demonstrated a close relationship to minute ventilation.

Low bone mineral density is prevalent in adults with cystic fibrosis (Haworth *et al* 1999). The level of daily physical activity undertaken by people with cystic fibrosis has been positively related to both bone mineral density and lung function (Elkin *et al* 2001). A Cochrane Review has been undertaken on 'Physical training for cystic fibrosis' (Bradley & Moran 2004). The review states that conclusions about the efficacy of physical training in cystic fibrosis are limited by the small size, short duration and incomplete reporting of most of the studies. Physical training, education and advice are part of the care package offered to most people with cystic fibrosis and there is a lack of evidence to actively discourage this. Further research is needed to assess comprehensively the net benefit of the addition of physical training to the care of people with cystic fibrosis.

Exercise has been shown to increase sputum production (Baldwin *et al* 1994) and to improve lung function in people with cystic fibrosis (Salh *et al* 1989; Zach, Oberwaldner & Hausler 1982; Zach, Purrer, & Oberwaldner 1981). There is increasing evidence that exercise and airway clearance are associated with a decrease in the decline

of forced expiratory volume in one second (Schneiderman-Walker *et al* 2000; Thomas, Cook, & Brooks 1995). The paper by Thomas *et al* was a meta-analysis, but the exercise programme in the three-year study by Schneiderman-Walker *et al* was a 20-minute programme undertaken at least three times per week at 70-80 percent of maximal heart rate.

Examples of the addition of an airway clearance regimen to physical exercise are demonstrated in this thesis. One subject was newly diagnosed with cystic fibrosis and a rugby player. On entry to the study his forced expiratory volume in one second was 86 percent predicted. Twelve months later, with the addition of an airway clearance technique (autogenic drainage) and having continued rugby and other sports, his forced expiratory volume was 104 percent predicted.

Another subject was a football referee, at national level, who experienced some abdominal discomfort about half way through the study and later sustained an ankle injury which meant he had to withdraw from both training and refereeing for a period of about two months. He continued with his airway clearance regimen of the flutter, but the deterioration in his lung function during the periods of comparative inactivity and the gradual increase when he returned to sport again are demonstrated in Figure 6.15 (p.198). These two cases represent an n=1 study (Mahon *et al* 1996), but highlight the benefits of both exercise and an airway clearance regimen in these two individuals.

Some people with cystic fibrosis may use exercise as a substitute for airway clearance, but there was no evidence of this from the diary cards (Table 6.22, p.195). Decreased adherence to airway clearance was not associated with an increase in exercise sessions. However Schneiderman-Walker *et al* (2000) noted that subjects on the exercise arm of

their study were less adherent to 'physiotherapy' and suggest that exercise, in their group of subjects, may have been used as a substitute.

Health related quality of life

Quittner *et al* (2004) examined patient satisfaction and impact on health related quality of life with the airway clearance regimens of postural drainage and percussion, flutter and high frequency chest wall oscillation. They concluded that patients were more satisfied with the flutter and high frequency chest wall oscillation than with postural drainage and percussion, and that this was related to a more positive quality of life. The flutter and high frequency chest percussion offered independence and not surprisingly improved quality of life. All the regimens in the airway clearance study of this thesis were undertaken independent of an assistant and in the sitting position. The health related quality of life questionnaires reflected no significant differences among the regimens.

Body mass index

There were no statistically significant differences among the regimens. The mean values for each group were within the ideal body weight range.

Borg

Borg's modification of his own scale with '(just noticeable)' associated with '0.5 very, very slight' (Borg 1982) should have been used in this airway clearance study, rather than the scale as published by Wilson and Jones (1989). It is unlikely however that it would have altered the results as the majority of the subjects were in the '4 somewhat severe' to '6' range for breathlessness and in the '3 moderate' to '5 severe' range for leg fatigue. In the Wilson and Jones study, where the subjects did not have known

respiratory or cardiac disease, the scores for breathlessness tended to be in the lower half, owing to the inbuilt ratio bias. All subjects used the Wilson and Jones' scale.

Imaging

At the time of setting up the protocol, the value of grading the chest radiographs for each subject was discussed with the Professor of Imaging at Royal Brompton Hospital. It was decided that imaging had little to offer in this airway clearance study.

Effects of gravity

The sitting position has been the position used. for many years, for airway clearance regimens other than the active cycle of breathing techniques. It had been intended to use this study as an opportunity to look at the effects of the head-down tipped position, in the same group of subjects, and this had been approved by the Ethics Committee. At the end of the 12-month study period, and before any change of airway clearance regimen, subjects were invited to continue the study regimen for a further two months, but to use the head-down tipped position. One or two kindly agreed to participate, but the majority declined. The subjects were aware of their own results and at the end of the 12-month period of doing their treatment in a sitting position they were not keen to revert to the head-down tipped position, even if only for two months. It became inappropriate to continue with this part of the study owing to poor recruitment. The exceptions were the two subjects, on the active cycle of breathing techniques, who withdrew from the study at six months to change back to the head-down tipped position. The two subjects were clinically stable. but said that they had been 'brought up to do it that way' and wished to revert to their original technique.

The effectiveness of an airway clearance regimen in the sitting position, for the patient in a stable clinical state, is possibly a consequence of the improvements in the physical health of these people. The side lying position may be indicated, but the head-down tipped position is infrequently of added value today (Cecins *et al* 1999). There is likely to be an increase in adherence to treatment as a consequence of the convenience of the sitting position. The early short term studies on the effectiveness of autogenic drainage (Miller *et al* 1995), cornet (Cegla 2000), flutter (Konstan, Stern, & Doershuk 1994) and positive expiratory pressure (Falk *et al* 1984) were undertaken using the sitting position. Gravity assisted positioning whether for the increase in regional ventilation to the dependent lung (Lannefors & Wollmer 1992) or the direct effects of gravity on mucus, or both, has remained the treatment of choice for the infant and young child, in some countries, until the child can begin to participate in huffing games or use a device such as the cornet or flutter. In many of the Scandinavian countries gravity assisted positioning has been replaced by physical activity for all age groups.

Adherence

The terms 'compliance', 'adherence' and 'concordance' are often used interchangeably. In Kettler *et al* (2002) Meichenbaum and Turk argue that there is an importance difference between compliance and adherence. They define compliance as 'the extent to which patients are obedient and follow the instructions, proscriptions, and prescriptions of health care professionals' and adherence as an 'active, voluntary, collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a desired preventative or therapeutic result'. The concept of concordance has been described as the frank exchange of information, negotiation and a spirit of cooperation (Mullen 1997).

In their review of the literature on adherence in adults with cystic fibrosis Kettler *et al* (2002) rank adherence to antibiotic treatment (oral or intravenous) as relatively high (80-95%), adherence to nebulised medications and pancreatic enzymes as moderate (65-80%) and adherence to vitamin therapy, dietary changes, exercise and physiotherapy as poor (40-55%) . Adherence to treatment in this thesis varied from 50-86 percent. Passero *et al* (1981) had identified an adherence of 40 percent with prescribed daily treatment of postural drainage and percussion with voluntary coughing. The differences between the study by Passero *et al* and the study of this thesis include the use of a regimen independent of an assistant, the use of the sitting position as opposed to the head-down tipped position and the patient rather than the physiotherapist prescribing the number of treatment sessions.

It is interesting to note that the average number of treatment sessions recommended by the patients themselves was two per day. It is appreciated that all subjects on a study 'do well'. Adherence to treatment, by the study patients, may have been influenced by their monthly physiotherapy appointments. This may indicate that an increase in the frequency of physiotherapy reviews (every two to three months) may increase adherence to treatment. This study does not answer the question as to whether a change of regimen, at intervals, will increase adherence to treatment.

Patients' perceptions of both the importance of an airway clearance technique and compliance increase with disease severity (Oermann *et al* 2001). This had also been identified by Carr *et al* (1996). In the questionnaire of Carr *et al*, a number of the patients said that they would use an airway clearance technique when they were unwell. When people are well and if there are no immediately detectable benefits, it is difficult to continue with something that does not cause an immediate change in one's feeling of

health or well-being (Hardy *et al* 1994) and yet it is in those with a high percent predicted forced expiratory volume in one second that a regimen of an airway clearance technique and physical exercise (sport) may lead to significant improvements in lung function with consequent improvements in morbidity and mortality.

It is important to remember that airway clearance is only one of a number of treatments that people with cystic fibrosis are asked to undertake by the multidisciplinary cystic fibrosis team. The more efficient and more user-friendly the regimen and the higher the rating of perceived benefit, the more likely the treatment is to be undertaken.

Recent publications

Accurso *et al* (2004) undertook a 3-year randomised controlled study to assess the long term effects of the airway clearance techniques of postural drainage and percussion, flutter and high frequency chest wall oscillation. Twenty cystic fibrosis centres, in the United States of America, took part. One hundred and sixty-six individuals entered the study, but 56 (33.7%) withdrew. In comparison 22 subjects (29%) withdrew, or were withdrawn, from the single centre airway clearance study of this thesis. From the study by Accurso *et al*, 15 withdrew on the day of randomisation after receiving their randomisation assignment. These 15 had been randomised either to the flutter or to postural drainage and percussion. In the subjects who participated for at least 60 days, there were differences in the percentage dropouts from each arm. The postural drainage and percussion regimen lost 51.1%, flutter lost 25.5% and high frequency chest wall oscillation lost 8.8%.

The most common reasons given for discontinuing (Accurso *et al* 2004) were moved or lost to follow up (n=13), lack of time (n=7), preferred another therapy (n=4), or

decrease in health or lung function (n=4). As stated by the authors, the uneven distribution of the dropouts across the treatment arms compromised the generalisability of the study and the trial was ended early. At the time the study was terminated, the duration of study participation ranged from 1.3 to 2.8 years. The conclusion was that the participants were more likely to accept the use of high frequency chest wall oscillation. The outcome measures of lung function have yet to be published, but from personal communication (Accurso 2004) there was a reduction in forced expiratory volume in one second (FEV_1), as a percent of predicted FEV_1 of -0.67 for postural drainage and percussion, -1.68 for the flutter and -1.34 for high frequency chest wall oscillation.

There are similarities and differences between the study by Accurso *et al* (2004) and the airway clearance study of this thesis. The study from the United States of America was multi-centre with 20 cystic fibrosis centres participating. This thesis was a single centre study. Accurso *et al* had hoped to recruit 180 patients and 166 entered the study over 2.8 years. The single centre study had hoped to recruit 150 patients and 75 entered over 3.5 years. Of the 166 patients who entered the Accurso *et al* study, 56 (33.7%) withdrew and 9% on receipt of their randomisation assignment. In comparison, in the study of this thesis, 22 subjects (29%) withdrew, or were withdrawn, from the single centre airway clearance study of one year and all entered and participated in the first assessment and introduction to the regimen.

The study of this thesis did not include postural drainage and percussion as it had been shown to be less effective and more time consuming than the active cycle of breathing techniques (Pryor *et al* 1979). High frequency chest wall oscillation (the 'Vest') (Warwick and Hansen 1991) had been considered as one of the regimens for the thesis, but the cost of a 'Vest' was over £5000 at the time of starting the study representing

more than £150,000 which was not available and the commercial companies from which the 'Vest' can be purchased would neither loan nor provide 'Vests' for the purpose of the study.

Accurso *et al* had included children (7 – 12 year olds: n=86, 13 – 17 year olds: n=44 and 18 years and over; n=36). It is not possible to ascertain how many 16 and 17 year olds were in the study but at least 36 were adults. In the study of this thesis the 75 subjects were adults (16 years of age and over, with a mean age of 28.7 years).

It would seem that both single centre and multi-centre airway clearance trials experience similar problems of recruitment and retention in long term studies.

Which technique for which patient?

It was hoped to identify objective indicators as to when a particular regimen may be recommended (Lapin 2000), but none were identified during the study period. This is evidence in support of international practice. Each regimen can and should be adapted to suit the individual patient and each patient should be able to adapt his / her regimen at the time of each treatment session and within a treatment session. It is important that the physiotherapist is familiar with the airway clearance regimen or regimens he / she is teaching and with the available evidence in support of the regimen. The patient should establish an effective and efficient regimen of his / her choosing, and should know how to adapt the regimen as necessary. 'Patient satisfaction and perceived efficacy are probably intimately related to adherence to a technique' (Lapin 2000).

This is supported by Langenderfer's (1998) findings: 'Which alternative to recommend depends on the ability, motivation, preference, needs, and resources of each patient.'

Langenderfer also says that the more elaborate and expensive devices. for example high frequency chest compression and intrapulmonary percussive ventilation can be used to assist mucus clearance in patients who lack the ability to perform the simpler techniques.

The impression, from subjects on the study of the thesis, is that the selection of a regimen is a personal preference phenomenon. At the end of the study period, or when a subject withdrew from the study, he / she was invited to try the other four regimens. On trying each of the regimens, the subject quickly (within one treatment session) identified with one, but no objective indicators could be ascertained.

The airway clearance techniques available to patients may be determined by the skills of the therapist (Hardy *et al* 1994) and the financing of health care provision. However if several techniques appear to be equally effective it is appropriate to let the patient select his / her regimen of choice. If ongoing research proves that several of the airway clearance techniques are equivalent, the more expensive techniques are unjustifiable (Hardy *et al* 1994).

This study, 'A comparison of five airway clearance techniques in the treatment of people with cystic fibrosis' provides additional evidence for international practice and concurs with the evidence available. The thesis did not attempt to answer the question as to which regimen should be used during an acute pulmonary exacerbation of infection. The study does raise the question as to whether a more frequent review of physiotherapy techniques – airway clearance and exercise – would increase adherence to treatment, and an effective airway clearance regimen may reduce the perception of breathlessness.

Chapter VIII. Summary

Strengths

- This is the largest randomised controlled trial on airway clearance, in adults with cystic fibrosis, from a single cystic fibrosis centre therefore minimising differences in the medical management of the subjects and interpretation of the airway clearance regimens.
- The study has involved the original proponents of the regimens of the active cycle of breathing techniques, autogenic drainage, cornet, flutter and positive expiratory pressure, in order to study the regimens as originally described.
- It is a long term study over a period of one year. Many airway clearance studies have been short term, either single treatments or carried out over a period of one or two days to ascertain safety. Long term studies are required to study the effectiveness of the regimens over time.
- It is an *in vivo* study. Many studies have looked at the effects of the different airway clearance techniques *in vitro*.
- The outcomes of the study have begun to change clinical practice at Royal Brompton Hospital where many physicians and physiotherapists have favoured the head-down tipped position and the active cycle of breathing techniques (Table 6.25, p. 199).

Weaknesses

- There was no control arm in this study. This would have been ideal in theory but unethical in practice in those with established disease, as there is evidence that airway clearance is of benefit in the management of these people. The medical

consultants responsible for the adult patients' management were not willing to withdraw physiotherapy from this subject group. Had the physicians been in agreement, it is unlikely that the patients would have withheld all previously learned physiotherapy techniques for 12 months. The only ethically acceptable alternative today is a comparison among the airway clearance regimens for which there is evidence of effectiveness or the use of one of the recognised regimens as a control for a new and untested regimen.

- In five years it was not possible to achieve 16 completers in each study arm. To have continued the study for longer would have exposed it to biases from developments in medical management.
- Objective indicators as to when one particular regimen or regimens should be recommended for a particular patient could not be identified, but this is in keeping with current international practice where physiotherapists, physical therapists and patients familiar with the regimens can adapt the regimens throughout the disease process.
- The study does not answer the question as to whether a change of regimen would increase adherence to treatment.
- The study does not indicate the best regimen during an acute pulmonary exacerbation of infection or the best regimen for infants and children.

New Findings

- The study, from a single centre of adult patients, has demonstrated that the airway clearance regimens of the active cycle of breathing techniques, autogenic drainage, cornet, flutter and positive expiratory pressure are equivalent, over a

period of one year, in the primary outcome measure of forced expiratory volume in one second.

- The study provides evidence in support of current international practice where individual countries and individual centres tend to favour one or more of the regimens.
- There was a trend for the decline in forced expiratory volume in one second using the flutter regimen to be less than that of the other regimens. This differs from the study by McIlwaine *et al* (2001) where subjects on the flutter arm of their study had a significant fall in forced expiratory volume in one second from six to 12 months, when compared with the positive expiratory pressure regimen.
- The selection of an airway clearance regimen is probably a personal preference phenomenon and a patient is more likely to adhere to a regimen of his / her choosing.
- A device may increase adherence to treatment in the short term, but there was no evidence to support an increase in adherence to treatment in the long term.
- The time taken for an average treatment using autogenic drainage is longer than that using the flutter.
- The sitting position for airway clearance can be recommended for most people with cystic fibrosis in a stable clinical state, but individual assessment and re-assessment is imperative.
- It would seem appropriate to teach, initially, a regimen which is independent of a device (active cycle of breathing techniques or autogenic drainage). If finance is available, it may then be appropriate to offer the patient the choice of a device (comet, flutter or positive expiratory pressure) as an alternative or to be used in combination.

- The null hypothesis was confirmed: there are likely to be no significant differences among the regimens of the active cycle of breathing techniques, autogenic drainage, comet, flutter and positive expiratory pressure.

These findings, in adults, should not be extrapolated to patients during an acute exacerbation of pulmonary infection or to the treatment of infants and young children.

The Future

- Randomised controlled trials would seem essential in research of airway clearance if studies are to be recognised by databases such as Cochrane and other systematic reviews, which are influencing evidence based practice today.
- Long term rather than short term studies are required.
- Multi-centre studies would improve the power of a study.
- New measurement tools for example lung clearance indices as measurements of ventilation inhomogeneities (Kraemer *et al* 2005), non-invasive chest wall imaging techniques which allow calculation of lung volumes, lung compliance measurements and non-invasive measurements of arterial carbon dioxide may provide greater insight to any differences which may exist among the regimens.
- New research questions:
    - Which airway clearance regimen should be recommended for an acute exacerbation of a pulmonary infection?
    - Would a change of airway clearance regimen, at intervals, increase adherence to treatment?
    - Is patient selection of a regimen associated with personality type?

- Is high frequency chest wall compression equivalent to the active cycle of breathing techniques, autogenic drainage. cornet, flutter and positive expiratory pressure?
- Are the differences between the study by McIlwaine *et al* (2001) and the study of this thesis, regarding the regimens of the flutter and positive expiratory pressure, associated with the age of the subjects?
- Which techniques should be recommended for infants and children?
- Is the side lying position beneficial during an acute infection?
- Have the patients of this study continued with the same airway clearance technique in the long term?

Chapter IX. Conclusion

This study suggests that there are no differences among the airway clearance regimens of the active cycle of breathing techniques, autogenic drainage, cornet, flutter and positive expiratory pressure when used over a period of one year, in the sitting position, by adults with cystic fibrosis. To optimise adherence to treatment and consequently improvements in morbidity and mortality, the patient should be involved in the selection of his / her airway clearance regimen.

The findings of this study must be limited to people with cystic fibrosis. The study does not suggest that people with bronchiectasis not associated with cystic fibrosis or other conditions with excess bronchial secretions can effectively use an airway clearance regimen in the sitting position.

Cystic fibrosis can no longer be called a disease of childhood but longevity for people with cystic fibrosis, although still increasing, remains significantly less than that of the general population. An effective patient selected airway clearance regimen, together with exercise, may help to minimise the annual decline in lung function for people with cystic fibrosis and to optimise quality of life, especially in the early stages of loss of lung function.

Survival and quality of life for people with cystic fibrosis has improved, but the prognosis is still poor. Gene therapy, when developed, and other new treatments will benefit most those with the minimal lung destruction. Physiotherapy and in particular airway clearance will therefore remain an important component in the management of these people for the foreseeable future.

Appendices

Appendix 1. Modified shuttle test

Study No:

Visit:

AIRWAY CLEARANCE STUDY

MODIFIED SHUTTLE WALK TEST (MST)

1 2 3

4 5 6 7

8 9 10 11 12

13 14 15 16 17 18

19 20 21 22 23 24 25

26 27 28 29 30 31 32 33

34 35 36 37 38 39 40 41 42

43 44 45 46 47 48 49 50 51 52

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89 90 91 92 93 94 95 96 97 98 99 100 101 102

103 104 105 106 107 108 109 110 111 112 113 114 115 116 117

118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133

134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150

Patient's Name: _____

Date: _____

SaO_2: Pre (5 min) MST:_____ MST:_____ Post (5min) MST:_____

Heart Rate Pre:_____ MST:_____ Post:_____

Peak Heart Rate: MST:_____

Chest (Borg): Pre MST:_____ Post MST:_____

Legs (Borg): Pre MST:_____ Post MST:_____

No. Started to Run: _____

No. of Shuttles Completed: _____

Reason for Stopping:

Appendix 2. Short Form-36 questionnaire

HEALTH STATUS QUESTIONNAIRE (SF-36)

For office use

THE FOLLOWING QUESTIONS ASK FOR YOUR VIEWS ABOUT YOUR HEALTH. HOW DO YOU FEEL AND HOW WELL YOU ARE ABLE TO DO YOUR USUAL ACTIVITIES. IF YOU ARE UNSURE ABOUT HOW TO ANSWER ANY QUESTION, PLEASE GIVE THE BEST ANSWER YOU CAN AND MAKE ANY COMMENTS IN THE SPACE AVAILABLE AFTER QUESTION 10.

Please tick one

1. In general would you say your health is:

- Excellent ◯
- Very good ◯
- Good ◯
- Fair ◯
- Poor ◯

2. Compared to one year ago, how would you rate your health in general now?

- Much better now than one year ago ◯
- Somewhat better now than one year ago ◯
- About the same ◯
- Somewhat worse now than one year ago ◯
- Much worse now than one year ago ◯

HEALTH AND DAILY ACTIVITIES

For office use

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

Please tick one circle

		Yes, limited a lot	Yes, limited a little	No, not limited at all	
a.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○	☐
b.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	○	○	○	☐
c.	Lifting or carrying groceries	○	○	○	☐
d.	Climbing several flights of stairs	○	○	○	☐
e.	Climbing one flight of stairs	○	○	○	☐
f.	Bending, kneeling or stooping	○	○	○	☐
g.	Walking more than a mile	○	○	○	☐
h.	Walking half a mile	○	○	○	☐
i.	Walking 100 yards	○	○	○	☐
j.	Bathing and dressing yourself	○	○	○	☐

For office use

4. During the <u>past 4 weeks,</u> have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

Answer Yes or No to each question

	YES	NO	
a. Cut down on the <u>amount of time</u> you spent on work or other activities	○	○	□
b. <u>Accomplished less</u> than you would like	○	○	□
c. Were limited in the <u>kind</u> of work or other activities	○	○	□
d. Had <u>difficulty</u> performing the work or other activities (e.g. it took extra effort)	○	○	□

5. During the <u>past 4 weeks,</u> have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

Answer Yes or No to each question

	YES	NO	
a. Cut down on the <u>amount of time</u> you spent on work or other activities	○	○	□
b. <u>Accomplished less</u> than you would like	○	○	□
c. Didn't do work or other activities as <u>carefully</u> as usual	○	○	□

For office use

6. During the <u>past 4 weeks,</u> to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Please tick one

- Not at all ○ ☐
- Slightly ○ ☐
- Moderately ○ ☐
- Quite a bit ○ ☐
- Extremely ○ ☐

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

- None ○ ☐
- Very mild ○ ☐
- Mild ○ ☐
- Moderate ○ ☐
- Severe ○ ☐
- Very severe ○ ☐

8. During the <u>past 4 weeks,</u> how much did <u>pain</u> interfere with your normal work (including work both outside the home and housework?

- Not at all ○ ☐
- A little bit ○ ☐
- Moderately ○ ☐
- Quite a bit ○ ☐
- Extremely ○ ☐

For office use

YOUR FEELINGS

9. These questions are about how you feel and how things have been with you during the past month. *(For each question, please indicate the one answer that comes closest to the way you have been feeling)*

Please tick one circle

How much time during the past month:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time	
a. Did you feel full of life	○	○	○	○	○	○	□
b. Have you been a very nervous person?	○	○	○	○	○	○	□
c. Have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○	○	□
d. Have you felt calm and peaceful?	○	○	○	○	○	○	□
e. Did you have a lot of energy?	○	○	○	○	○	○	□
f. Have you felt downhearted and low?	○	○	○	○	○	○	□
g. Did you feel worn out?	○	○	○	○	○	○	□
h. Have you been a happy person?	○	○	○	○	○	○	□
i. Did you feel tired?	○	○	○	○	○	○	□
j. Has your health limited your social activities (like visiting friends or close relatives)?	○	○	○	○	○	○	□

For office use

10 Please choose the answer that best describes how <u>true</u> or <u>false</u> each of the following statements is for you.

	Please tick one circle					
	Definitely true	Mostly true	Not sure	Mostly false	Definitely false	
a. I seem to get ill more easily than other people	○	○	○	○	○	☐
b. I am as healthy as anybody I know	○	○	○	○	○	☐
c. I expect my health to get worse	○	○	○	○	○	☐
d. My health is excellent	○	○	○	○	○	☐

COMMENTS

Appendix 3. Transformation of raw scores for the Short Form-36

Each item is recoded e.g. Question 6:

During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Response Choices	Precoded Item Value	Final Item Value
Not at all	1	5
Slightly	2	4
Moderately	3	3
Quite a bit	4	2
Extremely	5	1

The scale is scored to give a high score indicative of better social functioning. The scoring is available from the *SF-36 Health Survey: manual & interpretation guide* (Ware, Snow & Korinski 2000).

These raw scores are 'transformed' to a 0 to 100 scale:

Transformed scale = [(Actual raw score – lowest *possible* raw score) / *Possible* raw score range] x 100.

The lowest and highest possible raw scores should also be used for checking the accuracy of the raw score data. No score should be outside the possible raw score range (Ware, Snow & Korinski 2000):

Scale	Sum Final Item Values *(after recoding items as in Tables 6.1-6.8)*	Lowest and highest possible raw scores	Possible raw score range
Physical Functioning	3a+3b+3c+3d+3e+ 3f+3g+3h+3i+3j	10, 30	20
Role–Physical	4a+4b+4c+4d	4, 8	4
Bodily Pain	7+8	2, 12	10
General Health	1+11a+11b+11c+11d	5, 25	20
Vitality	9a+9e+9g+9i	4, 24	20
Social Functioning	6+10	2, 10	8
Role–Emotional	5a+5b+5c	3, 6	3
Mental Health	9b+9c+9d+9f+9h	5, 30	25

Appendix 4. Chronic Respiratory Questionnaire

CHRONIC RESPIRATORY QUESTIONNAIRE

FIRST ADMINISTRATION, 7 POINT SCALE

INTERVIEWER FORM

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about how short of breath you have been, how tired you have been feeling and how your mood has been.

1. I would like you to think of the activities that you have done during the last 2 weeks that have made you feel short of breath. These should be activities which you do frequently and which are important to your day-to-day life. Please list as many activities as you can that you have done during the last 2 weeks that have made you feel short of breath.

   [CIRCLE THE NUMBER ON THE ANSWER SHEET ADJACENT TO EACH ACTIVITY MENTIONED. IF AN ACTIVITY MENTIONED IS NOT ON THE LIST, WRITE IT IN, IN THE RESPONDENT'S OWN WORDS, IN THE SPACE PROVIDED.]

   Can you think of any other activities you have done during the last 2 weeks that have made you feel short of breath?

   [RECORD ADDITIONAL ITEMS]

2. I will now read a list of activities which make some people with lung problems feel short of breath. I will pause after each item long enough for you to tell me if you have felt short of breath doing that activity during the last 2 weeks. If you haven't done the activity during the last 2 weeks, just answer "NO". The activities are:

   [READ ITEMS, OMITTING THOSE WHICH RESPONDENT HAS VOLUNTEERED SPONTANEOUSLY. PAUSE AFTER EACH ITEM TO GIVE RESPONDENT A CHANCE TO INDICATE WHETHER S/HE HAS BEEN SHORT OF BREATH WHILE PERFORMING THAT ACTIVITY DURING THE LAST WEEK. CIRCLE THE NUMBER ADJACENT TO APPROPRIATE ITEMS ON ANSWER SHEET.]

1. BEING ANGRY OR UPSET
2. HAVING A BATH OR SHOWER
3. BENDING
4. CARRYING, SUCH AS CARRYING GROCERIES
5. DRESSING
6. EATING
7. GOING FOR A WALK
8. DOING YOUR HOUSEWORK
9. HURRYING
10. MAKING A BED
11. MOPPING OR SCRUBBING THE FLOOR
12. MOVING FURNITURE
13. PLAYING WITH CHILDREN OR GRANDCHILDREN
14. PLAYING SPORTS
15. REACHING OVER YOUR HEAD
16. RUNNING, SUCH AS FOR A BUS
17. SHOPPING
18. WHILE TRYING TO SLEEP
19. TALKING
20. VACUUMING
21. WALKING AROUND YOUR OWN HOME
22. WALKING UPHILL
23. WALKING UPSTAIRS
24. WALKING WITH OTHERS ON LEVEL GROUND
25. PREPARING MEALS

3. A) Of the items which you have listed, which is the most important to you in your day-to-day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[READ THROUGH ALL ITEMS SPONTANEOUSLY VOLUNTEERED AND THOSE FROM THE LIST WHICH PATIENT MENTIONED]

Which of these items is most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

B) Of the remaining items, which is the most important to you in your day-to-day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[READ THROUGH REMAINING ITEMS]

Which of these items is most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

C) Of the remaining items, which is most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

D) Of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

E) Of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

[FOR ALL SUBSEQUENT QUESTIONS, ENSURE RESPONDENT HAS APPROPRIATE RESPONSE CARD IN FRONT OF THEM BEFORE STARTING QUESTION]

4. I would now like you to describe how much shortness of breath you have experienced during the last 2 weeks while doing the five most important activities you have selected.

A) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3A]** by choosing one of the following options from the card in front of you:
[GREEN CARD]

1 EXTREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH

B) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3B]** by choosing one of the following options from the card in front of you. **[GREEN CARD]**

1 EXTREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH

C) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3C]** by choosing one of the following options from the card in front of you. **[GREEN CARD]**

1 EXTREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH

D) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3D]** by choosing one of the following options from the card in front of you. **[GREEN CARD]**

1 EXTREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH

E) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3E]** by choosing one of the following options from the card in front of you. **[GREEN CARD]**

1 EXTREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH

5. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient? Please indicate how often during the last 2 weeks you have felt frustrated or impatient by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How often during the last 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by choosing one of the following options from the card in front of you **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

7. What about fatigue? How tired have you felt over the last 2 weeks? Please indicate how tired you have felt over the last 2 weeks by choosing one of the following options from the card in front of you. **[ORANGE CARD]**

1 EXTREMELY TIRED
2 VERY TIRED
3 QUITE A BIT OF TIREDNESS
4 MODERATELY TIRED
5 SOMEWHAT TIRED
6 A LITTLE TIRED
7 NOT AT ALL TIRED

8. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by choosing one of the following options from the card in front of you. **[YELLOW CARD]**

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

10. How much energy have you had in the last 2 weeks? Please indicate how much energy you have had by choosing one of the following options from the card in front of you. **[PINK CARD]**

1 NO ENERGY AT ALL
2 A LITTLE ENERGY
3 SOME ENERGY
4 MODERATELY ENERGETIC
5 QUITE A BIT OF ENERGY
6 VERY ENERGETIC
7 FULL OF ENERGY

11. In general, how much of the time did you feel upset, worried, or depressed during the last 2 weeks? Please indicate how much of the time you felt upset, worried, or depressed during the past 2 weeks by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How often during the last 2 weeks did you feel you had complete control of your breathing problems? Please indicate how often you felt you had complete control of your breathing problems by choosing one of the following options from the card in front of you. **[YELLOW CARD]**

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

13. How much of the time during the last 2 weeks did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by choosing one of the following options from the card in front of you. **[YELLOW CARD]**

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

14. How often during the last 2 weeks have you felt low in energy? Please indicate how often during the last 2 weeks you have felt low in energy by choosing one of the following options form the card in front of you. **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps? Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you felt worn out or sluggish? Please indicate how much of the time you felt worn out or sluggish by choosing one of the following options form the card in front of you. **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks? Please indicate how happy, satisfied or pleased you have been by choosing one of the following options from the card in front of you. **[GREY CARD]**

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 HAPPY MOST OF THE TIME
6 VERY HAPPY MOST OF THE TIME
7 EXTREMELY HAPPY, COULD NOT BE MORE SATISFIED OR PLEASED

18. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

19. In general, how often during the last 2 weeks have you felt restless, tense, or uptight? Please indicate how often you have felt restless, tense, or uptight by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

CHRONIC RESPIRATORY QUESTIONNAIRE

FOLLOW-UP, 7 POINT SCALE, INFORMED

INTERVIEWER FORM

You have previously completed a questionnaire(s) telling us about how you were feeling and how your lung disease was affecting your life. This is a follow-up questionnaire designed to find out how you have been getting along during the last **[INSERT LENGTH OF TIME SINCE LAST SEEN]**.

When you are answering the questions this time I will tell you the answer you gave us the last time. I would like you to give your answer today keeping in mind what you said the last time. For example, let's say that last time I asked you how short of breath you were while climbing stairs **[GIVE RESPONDENT GREEN CARD]** and you said "4 Moderate shortness of breath". If you were exactly the same today, you would answer 4 once again. If you were **more** short of breath you would choose 1, 2, or 3 and if you were **less** short of breath you would choose 5, 6, or 7.

[FOR QUESTIONS 4A TO 4E INSERT ACTIVITIES 3A TO 3E FROM FIRST ADMINISTRATION ANSWER SHEET]

4. I would now like you to describe how much shortness of breath you have experienced during the last two weeks while doing each of the five most important activities you have selected.

A) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3A]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

B) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3B]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

C) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3C]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

D) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3D]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

E) Please indicate how much shortness of breath you have had during the last 2 weeks while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3E]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

5. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient? Please indicate how often during the last 2 weeks you have felt frustrated or impatient by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

6. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

7. What about fatigue? How tired have you felt over the last 2 weeks? Please indicate how tired you have felt over the last 2 weeks by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [ORANGE CARD]**

8. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

9. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [YELLOW CARD]**

10. How much energy have you had in the last 2 weeks? Please indicate how much energy you have had by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [PINK CARD]**

11. In general, how much of the time did you feel upset, worried, or depressed during the last 2 weeks? Please indicate how much of the time you felt upset, worried, or depressed during the past 2 weeks by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

12. How often during the last 2 weeks did you feel you had complete control of your breathing problems? Please indicate how often you felt you had complete control of your breathing problems by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [YELLOW CARD]**

13. How much of the time during the past 2 weeks did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [YELLOW CARD]**

14 How often during the last 2 weeks have you felt low in energy? Please indicate how often during the last 2 weeks you have felt low in energy by choosing one of the following options form the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

15. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps? Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

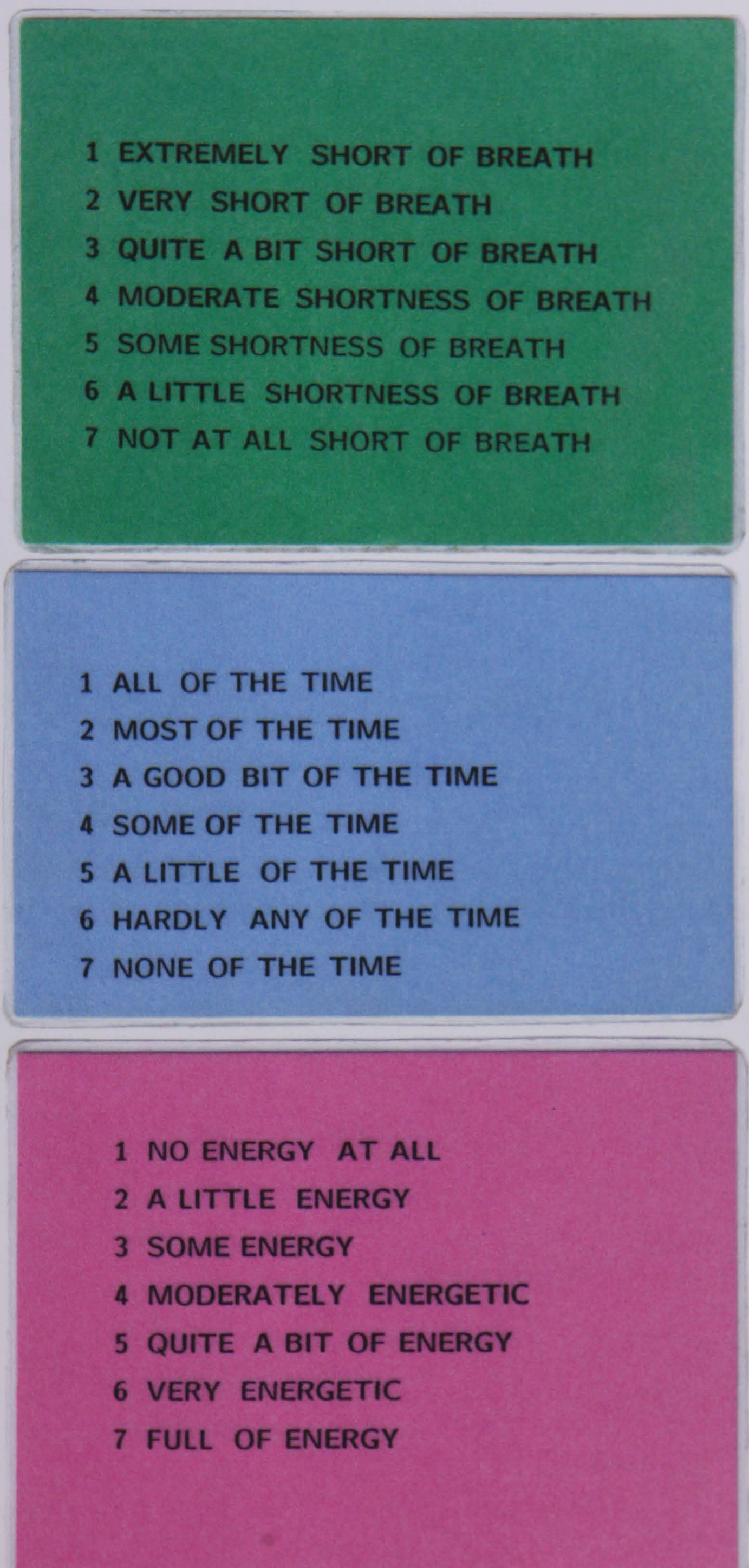
16. How often during the last 2 weeks have you felt worn out or sluggish? Please indicate how much of the time you felt worn out or sluggish by choosing one of the following options form the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

17. How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks? Please indicate how happy, satisfied or pleased you have been by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREY CARD]**

18. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the last 2 weeks you felt upset or scared when you had difficulty getting your breath by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

19. In general, how often during the last 2 weeks have you felt restless, tense, or uptight? Please indicate how often you have felt restless, tense, or uptight by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

Appendix 5. Response cards for Chronic Respiratory Questionnaire



Appendix 6. Missing values for the Chronic Respiratory Questionnaire

For the dyspnoea dimension, the following is a example of the calculation of a missing value:

	Baseline	Follow-up
a)	4	*
b)	3	2
c)	2	2
d)	4	2
e)	4	2

Follow-up score = [FU score CIBV + {(FU score CIBV / BL score CIBV) x BL score FUMI }] / 5

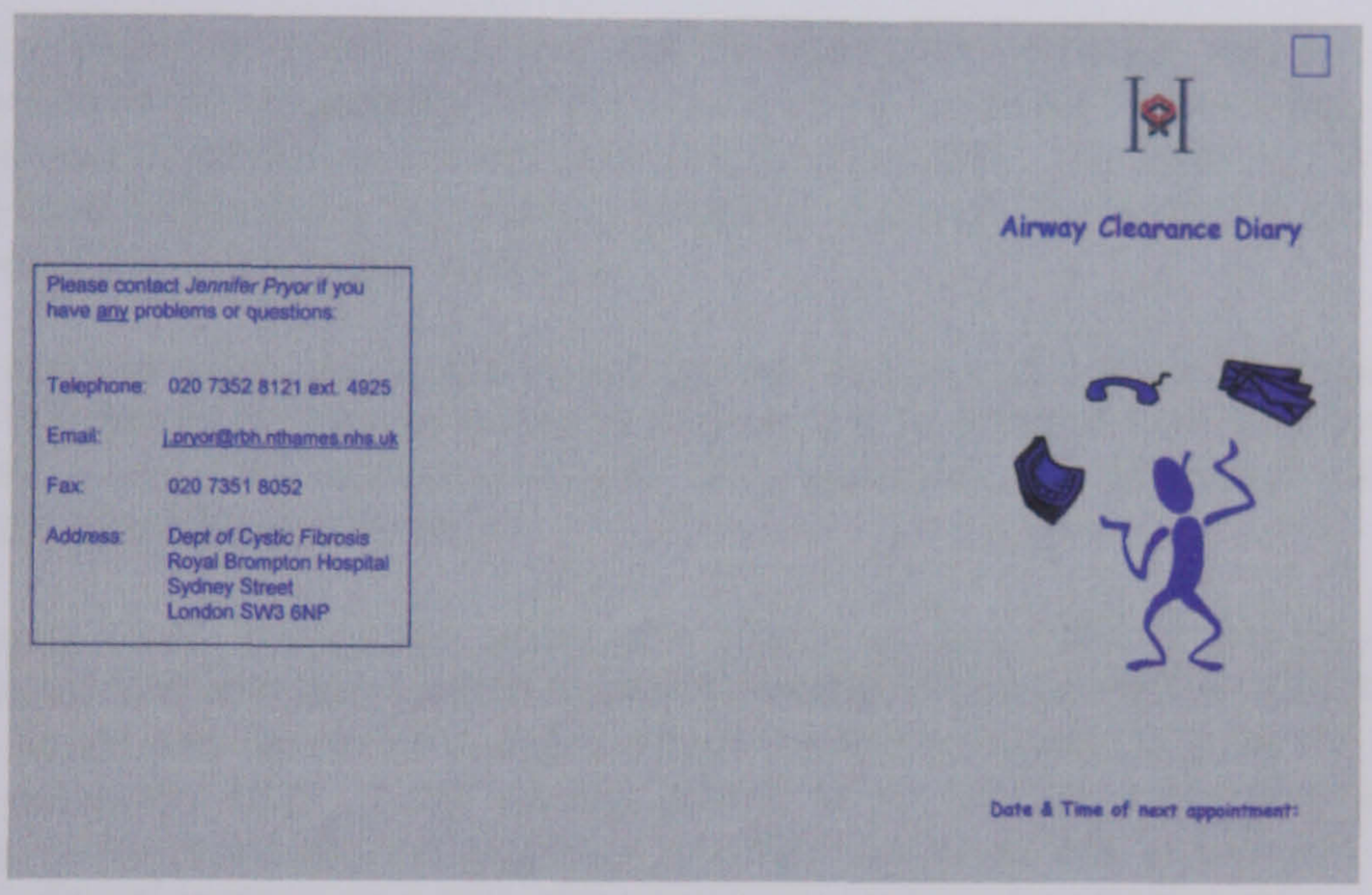
FU is follow-up. BL is the baseline.

CIBV is the sum of the responses the subject answered at both visits (baseline and follow-up). If (a) was the missing value, FU score CIBV would be the sum of (b), (c), (d) and (e) at the follow-up.

BL score CIBV is the sum of (b), (c), (d) and (e) at baseline and BL score.
FUMI the baseline score on the missing item.

Appendix 7. Diary





Name:

	Week:	Date:	Week:	Date:
1. In the last week how many treatments do you think you should have done each day?				
2. Approximately how many treatments did you miss in the last week?				
3. In the last week approximately how long did each of your treatment sessions take?				
4. What form of exercise have you taken this week?				
5. On how many days did you exercise?				
6. Has there been any change in your sputum this week?	Yes / No	If Yes, please describe:	Yes / No	If Yes, please describe:
7. Have you changed any of your drugs this week?	Yes / No	If Yes, please describe:	Yes / No	If Yes, please describe:
8. Was someone reminding / encouraging you to do your physiotherapy this week (*blow sick*)?	With every treatment / With a few treatments	With most treatments / With no treatments	With every treatment / With a few treatments	With most treatments / With no treatments
9. Have you any other comments?				

Appendix 8. Letter to prospective subject

Royal Brompton & Harefield NHS Trust
Sydney Street, London SW3 6NP Tel: 0171 352 8121 Fax: 0171 351 8473

Department of Cystic Fibrosis
Telephone extension: 4925 Email: j.pryor@rbh.nthames.nhs.uk

D D
Drayton Close
West Croydon
Surrey

25 June 1999 Our ref jp/let/001

Dear D

As you probably know, different people are using different airway clearance techniques for physiotherapy. We don't know which is the best one for you, to help to reduce your infections and to maintain your lung function. We are about to study the active cycle of breathing techniques, autogenic drainage, the cornet, flutter and PEP and would like to invite you to join us.

If you are interested, you would be randomised to one of the above regimens for one year. You would be trained in the technique if it is different from the one you are currently using and monitored closely. Any expenses, for additional visits to the Hospital, would be met by us.

We need more information about the effects of the different airway clearance techniques and how they work in individual people. If you would like to be involved or if you would just like to know more about the study, please ring me on 0171 352 8121 extension 4925. If my answer phone is on, please leave your name and telephone number and I will ring back at a moment when it is convenient for you. If you would rather drop me a line, please do so and again I could ring you.

Thank you for giving this some thought. Professor Hodson and I realise how many studies you are asked to participate in and we are very appreciative of all the help you give us as we all endeavour to continue to improve treatments for people with cystic fibrosis.

I look forward to hearing from you.

With best wishes

Yours sincerely

Miss Jennifer A. Pryor
Research Fellow, Physiotherapy

Appendix 9. Form of Consent

Royal Brompton & Harefield NHS Trust & National Heart and Lung Institute

FORM OF CONSENT *ADULT PATIENT*

TITLE OF PROJECT:
Should any one airway clearance technique be recommended for patients with cystic fibrosis?

EXPLANATION OF PROJECT (Part 1):
As you probably know, different airway clearance techniques (chest physiotherapy) have developed in different parts of the world. Some countries have a preference for one and other countries use several of the techniques. At Royal Brompton Hospital we have used mainly the active cycle of breathing techniques, following our studies in the 1970's and '80's, and with which you may have helped.

In the long-term, one year, we do not know how different techniques of physiotherapy, for example the active cycle of breathing techniques (ACBT), will compare with autogenic drainage (AD), the Cornet, the Flutter or the positive expiratory pressure mask (PEP). We would like to compare these techniques, used in the sitting position, to see if they are equally as good and we would like to ask you to consider taking part in this study.

If you would be willing you would be allocated, randomly, to one of the above airway clearance treatments (ACBT, AD, Cornet, Flutter or PEP) and trained in this one by a physiotherapist who is familiar with the technique. To study the techniques we would need to monitor you closely and this would involve additional visits to Royal Brompton Hospital to see the physiotherapist and to test your lung function, oxygen saturation and modified shuttle walk. The physiotherapist would check your technique after the first fortnight and then monthly for the next 12 months. We would like you to fill out a questionnaire about your health at the beginning, middle and end of the study and one at the time of your monthly visits. Whenever possible we would combine these visits with your clinic appointments and your travel expenses would be covered by us.

Your physiotherapist will be available should you have any queries during the study period. The number to ring is 0171 352 8121 and ask for either extension 4925 or bleep number 7313.

Thank you very much for thinking about taking part in this study. We would be happy to discuss any aspect of it and to answer any questions you may have. Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected.

Signed by the person in charge of the Project _____ Date 15/6/99.

The Ethics Committee of the Royal Brompton & Harefield NHS Trust/National Heart & Lung Institute has approved the above statement.
Signed by the Chairman/Representative of the Committee

_____ Date 15/6/99

DOCTOR'S DECLARATION

I have explained the project to the Participant as outlined above in the presence/absence* of a Witness**

Signed _____ Date _____ Time _____

* delete as appropriate

** every effort should be made to give the explanation in the presence of a witness

Protocol Reference Number: 99-043

Appendix 10. Regimens

The authorised, signed regimen is followed by the regimen which was given to the patient.

Active Cycle of Breathing Techniques

The active cycle of breathing techniques (ACBT) is used to mobilize and clear excess bronchial secretions (Pryor et al 1979). The components of the ACBT are breathing control, thoracic expansion exercises and the forced expiration technique. The regimen is flexible, adapted to suit the individual and can be used in the elderly, the young, the sick and the fit. It was first documented by Thompson and Thompson in 1968. The ACBT can be used either independent of an assistant or with an assistant.

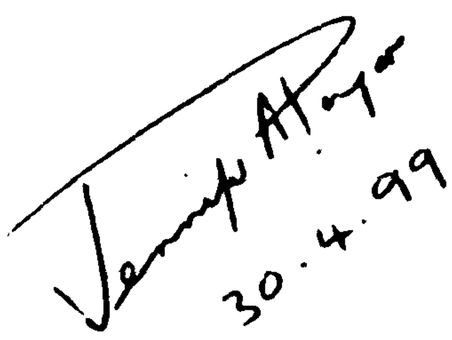
Breathing control (Webber, Pryor 1993) is normal gentle breathing at tidal volume, using the lower chest with relaxation of the upper chest and shoulders. It is an essential part of the cycle to allow pauses for rest and to prevent any increase in airflow obstruction. The length of the pause is dependent on the individual patient's signs of airflow obstruction.

Thoracic expansion exercises are deep breathing exercises emphasising inspiration and with a quiet, unforced expiration. With an increase in lung volume the resistance to airflow via the collateral channels is reduced. Mobilization of secretions can be facilitated by air passing along these channels and behind secretions. In some patients a three second hold at the end of inspiration will augment this effect. Three to four thoracic expansion exercises may be combined with chest shaking or chest clapping, and are followed by breathing control. Chest clapping and shaking appear to be helpful in some patients, but are unnecessary in others.

The forced expiration technique is one or two huffs combined with breathing control. Huffing continued down to a low lung volume will help to mobilize and clear the more peripherally situated secretions. When secretions reach the larger, more proximal airways they are cleared by a huff or cough at a high lung volume. The length of the huff and force of contraction of the muscles of expiration should be altered to maximize clearance of secretions.

The concept of the equal pressure point (West 1992), with collapse and compression downstream (towards the mouth) of the equal pressure point, explains the mechanism of the effectiveness of the forced expiratory manoeuvre of a huff or cough in airway clearance.

The ACBT can be introduced as huffing games from the age of about two years, and from the age of about eight or nine years the child can begin to take some responsibility for his/her own treatment, gradually becoming independent.



Active Cycle of Breathing Techniques (ACBT)

The ACBT is a cycle of the techniques of breathing control, thoracic expansion exercises and the forced expiration technique.

Breathing control is normal gentle breathing using the lower chest and with relaxation of the upper chest and shoulders. It is important to allow pauses for rest and to prevent any tightening of your airways. The length of the pause will vary depending on how tight your airways are feeling.

Thoracic expansion exercises are deep breathing exercises emphasising breathing in. Breathing out is quiet and relaxed. Holding your breath for two or three seconds, at the end of the breath in, may further help to loosen secretions. After 3 or 4 thoracic expansion exercises go back to your breathing control.

The forced expiration technique is 1 or 2 huffs combined with breathing control. Huffing down to a low lung volume will help to mobilise and clear the more peripherally situated secretions. When secretions reach the upper airways you can clear them with a huff or cough. The length of the huff and force you use should be varied to get the best airway clearance.

- Sit in a comfortable, well-supported position
- The breathing control, thoracic expansion exercises and forced expiration technique should be used flexibly and repeated until your huff becomes dry sounding and non-productive or it is time for a rest
- A minimum of ten minutes is recommended
- Self chest clapping and / or chest shaking may be used if helpful.

Department of Cystic Fibrosis (J.A.P.)
Royal Brompton & Harefield NHS Trust
July 1999

AUTOGENIC DRAINAGE TECHNIQUE 2

The Expiratory Force
is Balanced
so that Expiratory Flow reaches the Highest Rate possible
without causing Airway Compression

A substancial Volume of air
is Breathed OUT at High Velocity
to Enhance the Shear forces.(Wind)

In mild to severe cases of CF
Breathing OUT is like a Sigh
***

Breathe OUT in a proper way.
Mucus can be Heard.
Hands on Chest-Feel mucus Vibrating.
High Frequency=Small Airways
Low Frequency=Large Airways
***

Gradually
increase the Fonctional Tidal Volume
from Lower to Higher lung volume Breathing Levels.
***

Use the FEEDBACK!
Feel,Hear&Proprioceptive info.
***

Jean Chevaillier,Lynn Gumery,Alison Stracham(1996)

14/04/99

AUTOGENIC DRAINAGE TECHNIQUE

Before starting AD, clear upper airways - Nose and Throat

1 **BREATH STIMULATING POSITION -** Sitting upright

2 **BREATHING IN –**

- **Slowly breathe in** the necessary volume, **Keeping the upper airways open**
- Use **diaphragmatic breathing** (breathing control) or lower chest if possible
- **Hold breath** for 2,3 or 4 seconds, keeping all upper airways open to encourage the even filling of all parts of the lungs. During this phase air gets behind the secretions
- **Tidal Volume** – This is altered depending on where the mucus is ie; Low, middle and high lung volume

3 **BREATHING OUT –**

- Breathe out with the upper airways open (glottis, throat and mouth)
  Do not slow down expiratory flow
- The expiratory force is balanced so that expiratory flow reaches the highest rate possible without causing airway compression
- A substantial volume of air is breathed out at high velocity to enhance the shear forces (wind). Breathing out is like a sigh.
- **Breathe out in a proper way -** Mucus can be heard.
  Place hands on chest – feel the mucus vibrating –
  High frequency = small airways, Low frequency = large airways

4 **REPEAT CYCLE –**

- Inhale slowly avoiding mucus moving back peripherally

5 **CONTINUE TO BREATHE –**

- Until secretions start to collect by moving upwards
- Gradually increase the Functional Tidal Volume from lower to higher lung volume breathing levels
- Collect mucus and evacuate by 1 or 2 huffs or an effective cough
- **Use FEEDBACK !** Utilise proprioception ie; FEEL, HEAR

Update June 1999 – Jean Chevaillier, Lynne Gumery, Alison Strachan, Jo Sheldon

Regimen for the RC-Cornet®(Cornet)

Position
The RC-Cornet can be used in any position,as indicated on assessment.
One day should be sufficient to master the technique.

Technique

- The subject breathes in through his/her nose and out through the Cornet.

- The Cornet is used for 10-15 minutes to loosen and mobilise secretions; breathing starts at tital volume and is increased to about vital capacity in accordance with the physical possibilities of the patient.

- The pressure and flow can be altered by twisting the mouthpiece until an optimal effect is felt.This will vary from patient to patient.
  Recommended for CF patients are positions III to IV.

- As secretions loosen they are cleared with coughing or huffing.

- Breathing control is used in between the more active breathing manoeuveres.

- **NB Neither chest shaking nor chest clapping is to be included.**

Cleaning and maintenance

- Clean the RC-Cornet at least once a day or if possible after each treatment: remove the inner rubber tube,insert the spatula and leave to air dry.

- Once a week,wash all parts in warm soapy water,rinse thoroughly and allow to dry.

- Once a year,replace the rubber tube.

Contraindications

- Pneumothorax
- Severe,acute haemoptysis

S 21 49

RC-Cornet® (Cornet)

- Sit in a comfortable, well-supported position
- Breathe in through your nose and out through the Comet
- Start by breathing at your normal rate and depth
- Intersperse your normal breathing with a few deeper breaths
- As secretions loosen they are cleared with huffing or coughing
- The pressure and flow can be altered by twisting the mouthpiece until an optimal effect is felt. This may vary, but positions III to IV are recommended
- Breathing control is used in between the more active breathing manoeuvres
- Use the Cornet for 10 - 15 minutes to loosen and mobilise secretions
- Neither chest shaking nor chest clapping is to be included.

Department of Cystic Fibrosis (J.A.P.)
Royal Brompton & Harefield NHS Trust
July 1999

"Flutter" Airway Clearance Therapy

The "Flutter" is a small handheld, pipe-shaped device with a hard plastic mouthpiece on one end, a plastic perforated cover at the other end and a high-density stainless steel ball resting in a plastic circular cone on the inside.

The effectiveness of the Flutter as a mucus-clearance device is based on its ability to:

- vibrate airways to loosen mucus from the inner lumen of the airway walls.
- Help maintain airways open during exhalation
- Create 'mini coughs' to promote mucus removal

Specific procedure for using the Flutter device

Using the correct procedure with the Flutter is critical to achieving successful results.

a. Sit upright with your back straight and head tilted slightly back (or) sit in a chair with your elbows resting on a table.

Stage 1 – Mucus loosening and mobilization

b. Slowly inhale beyond a normal breath, but do not fill lungs completely.
c. Hold breath for 2 to 3 seconds
d. Place Flutter in your mouth and exhale reasonably fast but not too forceful through the Flutter.
e. Adjust the 'tilt' of the Flutter to achieve the sensation of maximum vibration in your lungs.
f. Exhale beyond a normal breath, but do not empty your lungs completely.
g. Repeat steps (b through f) for approximately 5 to 10 breaths.

Stage 2 – Mucus elimination

h. Slowly inhale, filling lungs completely.
i. Hold breath for 2 to 3 seconds.
j. Place Flutter in your mouth and exhale forcefully and as completely as possibly.
k. Repeat steps (h through J) for 1 to 2 breaths.
l. Initiate a cough (or "huff" maneuver) to expectorate mucus.
m. Repeat full sequence (stage 1 and 2) until your lungs are clear.

From: 'Airway Clearance / Chest Physiotherapy'
J Bolek RRT, 9/13/98 (Document prepared for the Adult Cystic Fibrosis Advisory Committee)

Flutter

- Sit upright with your back straight and head tilted slightly back (or) sit in a chair with your elbows resting on a table.

Stage I - Mucus loosening and mobilization

- Slowly inhale beyond a normal breath, but do not fill your lungs completely. Hold your breath for 2 to 3 seconds

- Place the Flutter in your mouth and exhale reasonably fast but not too forcefully through the Flutter. Adjust the tilt of the Flutter to achieve the sensation of maximum vibration in your lungs. Exhale beyond a normal breath, but do not empty your lungs completely

- Repeat these steps for approximately 5 to 10 breaths.

Stage 2 - Mucus elimination

- Slowly inhale, filling lungs completely. Hold your breath for 2 to 3 seconds

- Place the Flutter in your mouth and exhale forcefully, and as completely as possible

- Repeat these steps for I to 2 breaths

- Huff and / or cough to clear secretions.

Repeat stages I and 2 until your lungs are clear.

Department of Cystic Fibrosis (J.A.P.)
Royal Brompton & Harefield NHS Trust
July 1999

iv. *Positive Expiratory Pressure (PEP)*

The rationale for positive expiratory pressure (PEP) treatment in Cystic Fibrosis is described in Andersen JB & Falk M. Chest Physiotherapy in the Pediatric Age Group. Respir Care 36; 546-522, 1991.

At the Danish Cystic Fibrosis Centre, Copenhagen, PEP treatment is administered as outlined below:

The PEP system (Astra Tech, Denmark) consists of a mask and a one-way valve to which expiratory orifice resistors can be attached. A manometer determining the correct PEP level can be inserted between the valve and the resistor. The diameter of the resistor used for treatment is determined for each individual patient to give a steady PEP of 10 - 20 cm H_2O during the middle part of expiration. This pressure should be maintained during tidal volume breathing with only slightly active expirations.

Treatment is carried out sitting in the upright position (babies are carried on the arm during treatment). A treatment session consists of periods of breathing with PEP followed by the forced expiration technique or cough.

The frequency and duration of each treatment is adapted to the needs of the individual patient. About 10 - 15 minutes twice a day is recommended during stable pulmonary disease.

Merete Falk & Mette Kelstrup
Physiotherapists
Department of Physiotherapy
Rigshospitalet
DK-2100 Copenhagen
Denmark

Telephone: 45-35-453545
Fax: 45-35-456717

Mette Kelstrup
11.3.99

Positive Expiratory Pressure (PEP)

- Sit in a comfortable, well-supported position with your elbows resting on eg a table

- Breathe in and out through the PEP mask using a slightly active expiration (10 – 20 cm H_20 during the middle part of expiration)

- Periods of breathing with the PEP mask (approximately 10 breaths) are followed by huffing or coughing as secretions are loosened

- Huffing and coughing are followed by breathing control

- 10 to 15 minutes twice a day is recommended and may be increased if necessary

- Neither chest shaking nor chest clapping is to be included.

Department of Cystic Fibrosis (J.A.P.)
Royal Brompton & Harefield NHS Trust
July 1999

Appendix 11. Cleaning instructions

Recommendations for cleaning the Cornet

After each use:

- Remove inner tube
- Insert spatula into inner tube and leave to air dry
- Leave outer casing to air dry

Daily:

- Disassemble
- Insert spatula into inner tube
- Wash thoroughly in warm water with washing up liquid
- Rinse in clean running water
- Dry thoroughly with kitchen paper and leave, disassembled, to air dry

Weekly

- Using a small bottle brush, clean inside of outer casing in warm water with washing up liquid
- Rinse in clean running water
- Dry thoroughly with kitchen paper and leave to air dry.

Recommendations for cleaning the Flutter

After each use:

- Dismantle, dry thoroughly with kitchen paper and leave, unassembled, to air dry

Daily:

- Dismantle, wash thoroughly in warm water with washing up liquid
- Rinse in clean running water
- Dry thoroughly with kitchen paper and leave, unassembled, to air dry.

Recommendations for cleaning the Positive Expiratory Pressure Mask

After each use:

- Separate mask, valve and resistor
- Dry each piece thoroughly with kitchen paper and leave, unassembled, to air dry

Daily:

- Separate mask, valve and resistor and remove rubber from mask case
- Wash each piece thoroughly in warm water with washing up liquid
- Dry thoroughly with kitchen paper and leave, unassembled, to air dry.

Appendix 12. Genotype

Genotype or Sweat Sodium (>70mmol / litre)				
ACBT	**AD**	**Cornet**	**Flutter**	**PEP**
DF508 / N	DF508 / DF508	DF508 / DF508	DF508 / DF508	DF508 / G551D
DF508 / DF508	DF508 / DF508	DF508 / N	DF508 / DF508	DF508 / N1303K
DF508 / DF508	DF508 / DF508	DF508 / N	DF508 / N	DF508 / DF508
DF508 / DF508	R1162X / R1162X	DF508 / DF508	DF508 / R1162X	DF508 / DF508
DF508 / DF508	DF508 / N	DF508 / DF508	DF508 / DF508	G551D / N
R347H / N	DF508 / DF508	DF508 / DF508	DF508 / DF508	DF507 / 1248+1G>A
DF508 / DF508	D508 / N	D508 / N	D508 / N	DF508 / N
D508 / N	DF508 / S549N	DF508 / N	Sweat sodium >70 mmol/litre	DF508 / DF508
DF508 / N	Sweat sodium >70 mmol/litre	D508 / N1303K	DF508 / DF508	DF508 / DF508
D508 / N	DF508 / DF508	DF508 / DF508	D508 / N	DF508 / G542X
Sweat sodium >70 mmol/litre	G551D / N	DF508 / DF508	DF508 / N	D508 / R553X
D508 / G542X	N / DF508	DF508 / DF508	DF508 / DF508	DF508 / DF508
Sweat sodium >70 mmol/litre	DF508 / DF508	DF508 / N	DF508 / DF508	D508 / G85E
DF508 / N	DF508 / N	DF508 / DF508	DF508 / N	G542X / 1717-IG>A
DF508 / G551D	DF508 / DF508	Sweat sodium >70 mmol/litre	DF508 / DF508	DF508 / DF508

Appendix 13. Dominant organism on entering the study

Dominant organism on entering the study				
	Number of subjects			
	Staphylococcus	***Pseudomonas aeruginosa***	***Burkholderia cepacia***	**Unknown**
ACBT	1	12	1	1
AD	3	9	3	0
Cornet	0	14	1	0
Flutter	6	8	1	0
PEP	2	13	0	0

Appendix 14. Co-existing conditions

Co-existing conditions		
	Number of subjects	
	Diabetes	**Other**
ACBT	1	
AD	5	
Cornet	2	Anorexia nevosa
Flutter	1	
PEP	5	

Appendix 15. Dornase alfa

Entered study on Dornase alfa Number of subjects	
ACBT	7
AD	6
Cornet	11
Flutter	7
PEP	8
Note: No subject was started on Dornase alfa during the study.	

Appendix 16. Pancreatic sufficiency

Pancreatic		
	Insufficient	**Sufficient**
ACBT	11	4
AD	12	3
Cornet	14	1
Flutter	10	5
PEP	14	1

Appendix 17. New referrals

Patients newly referred to Royal Brompton Hospital	
ACBT	3
AD	3
Cornet	2
Flutter	1
PEP	3
Total	12

Appendix 18. Individual values for forced expiratory volume in one second

FEV_1 (litres) for each subject using intention to treat, n = 65 (0 months and 12 months)		
ACBT (n=13)	**0 months**	**12 months**
	1.18	1.12
	1.41	1.53
	1.62	1.73
	2.50	2.26
	2.33	2.15
	3.03	2.89
	0.72	0.75
	2.80	2.75
	1.55	1.51
	3.40	3.57
	1.50	1.53
	2.68	2.27
	1.38	1.17
Mean ± SD	2.01 ± 0.82	1.94 ± 0.80

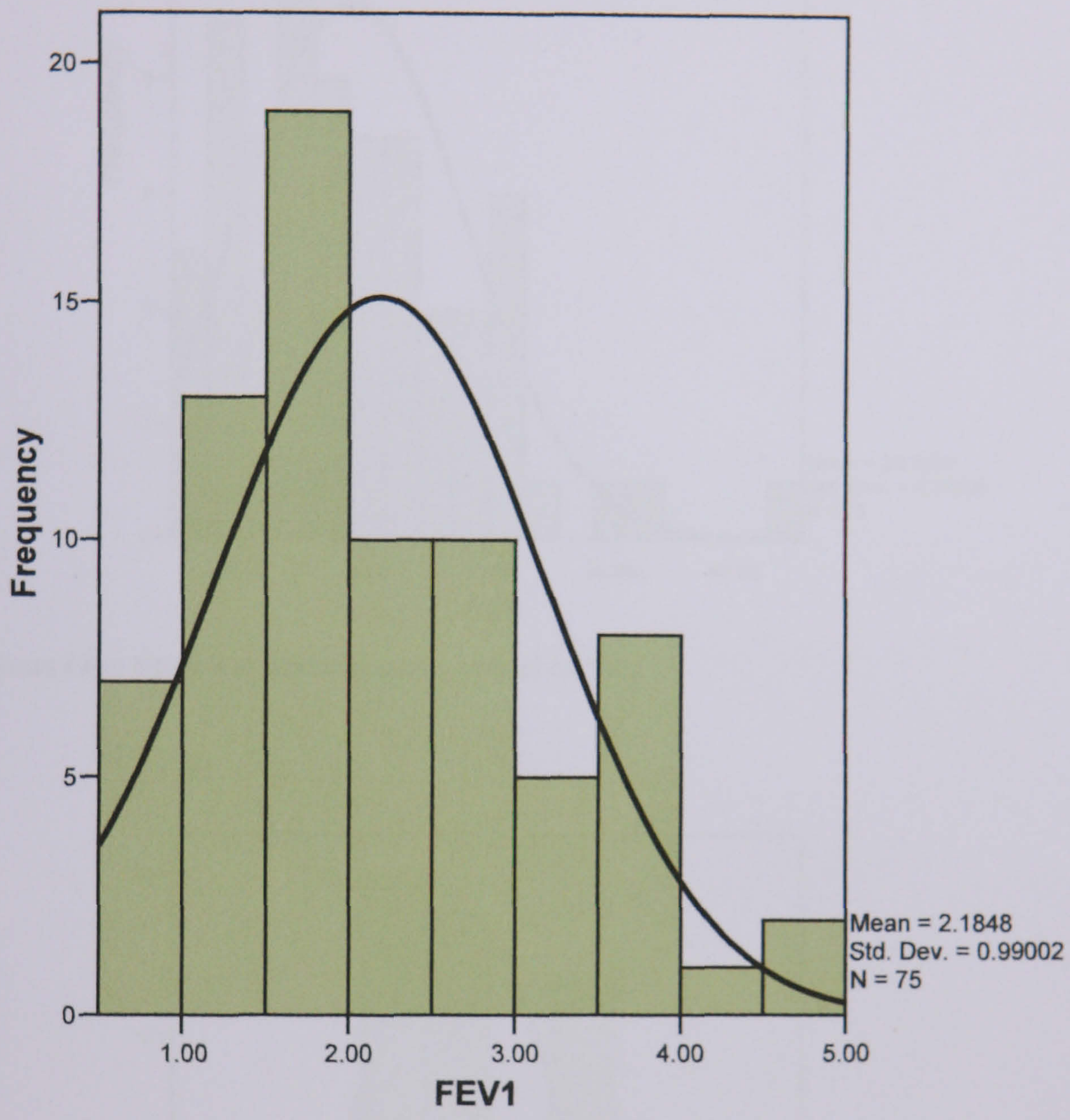
AD (n=13)	**0 months**	**12 months**
	1.15	1.23
	3.09	3.07
	1.49	1.56
	3.89	4.69
	0.84	0.85
	3.54	3.23
	2.43	2.25
	1.88	2.15
	1.59	1.61
	4.56	3.79
	4.53	4.09
	3.79	3.83
	2.07	2.00
Mean ± SD	2.68 ± 1.29	2.64 ± 1.22

Cornet (n=14)	0 months	12 months
	2.43	2.41
	0.83	0.79
	2.52	2.56
	1.67	2.00
	1.34	1.31
	2.81	2.79
	2.69	2.47
	1.58	1.49
	1.71	1.26
	0.82	0.73
	0.67	0.84
	1.84	1.73
	3.65	3.79
	2.44	2.37
Mean ± SD	1.93 ± 0.87	1.90 ± 0.89

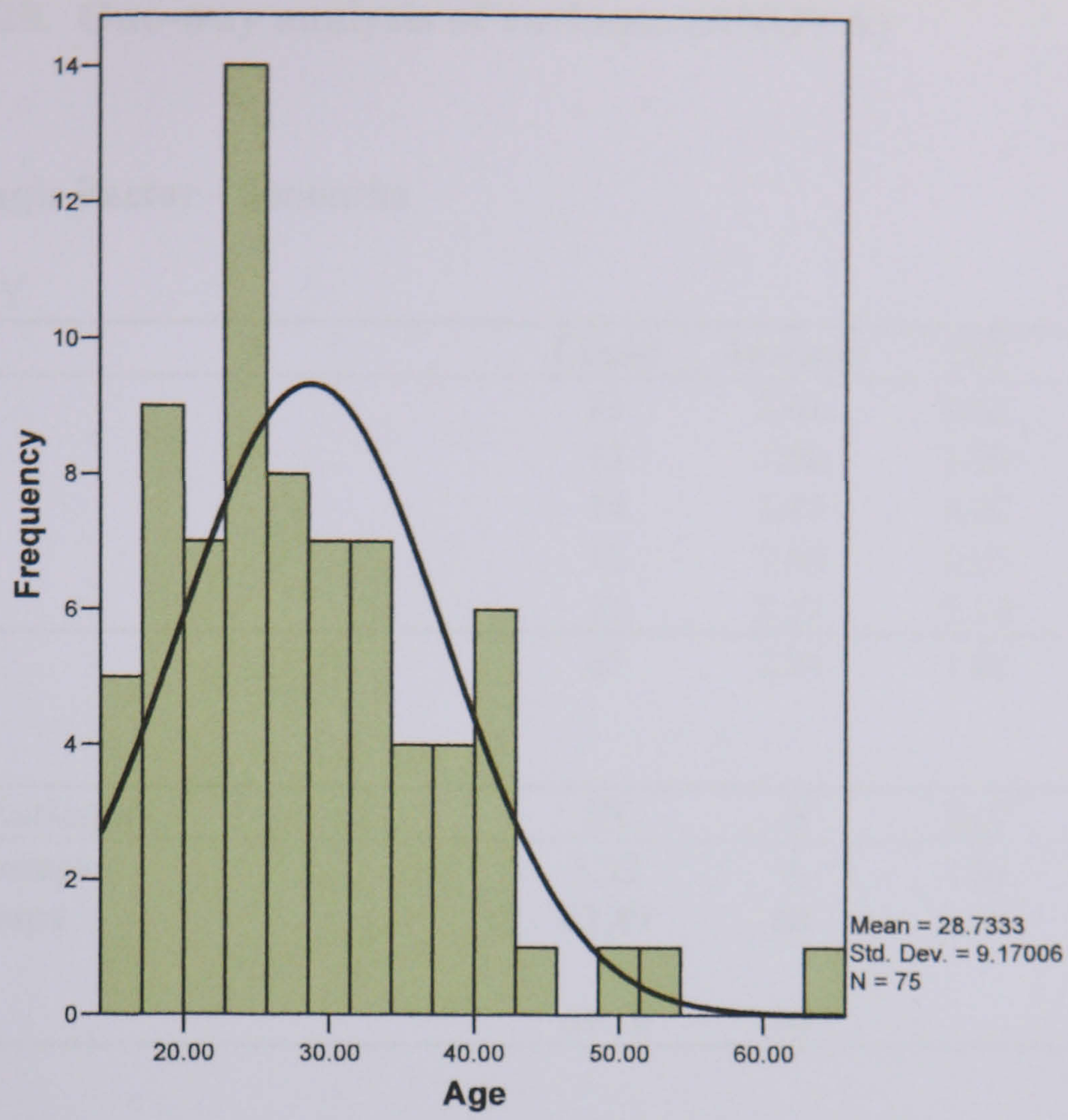
Flutter (n=12)	0 months	12 months
	1.63	1.66
	1.19	1.19
	3.36	3.43
	3.91	3.91
	2.39	2.07
	1.51	1.48
	1.90	1.98
	2.12	2.20
	2.58	2.59
	3.77	3.64
	3.58	3.42
	1.54	1.58
Mean ± SD	2.46 ± 0.94	2.43 ± 0.94

PEP (n=13)	0 months	12 months
	2.75	2.47
	4.48	4.28
	0.83	0.63
	1.72	1.46
	1.39	1.18
	2.78	2.41
	2.21	2.36
	3.46	3.37
	1.28	1.07
	1.08	1.06
	1.22	1.26
	3.54	3.66
	1.43	1.10
Mean ± SD	2.17 ± 1.14	2.02 ± 1.17

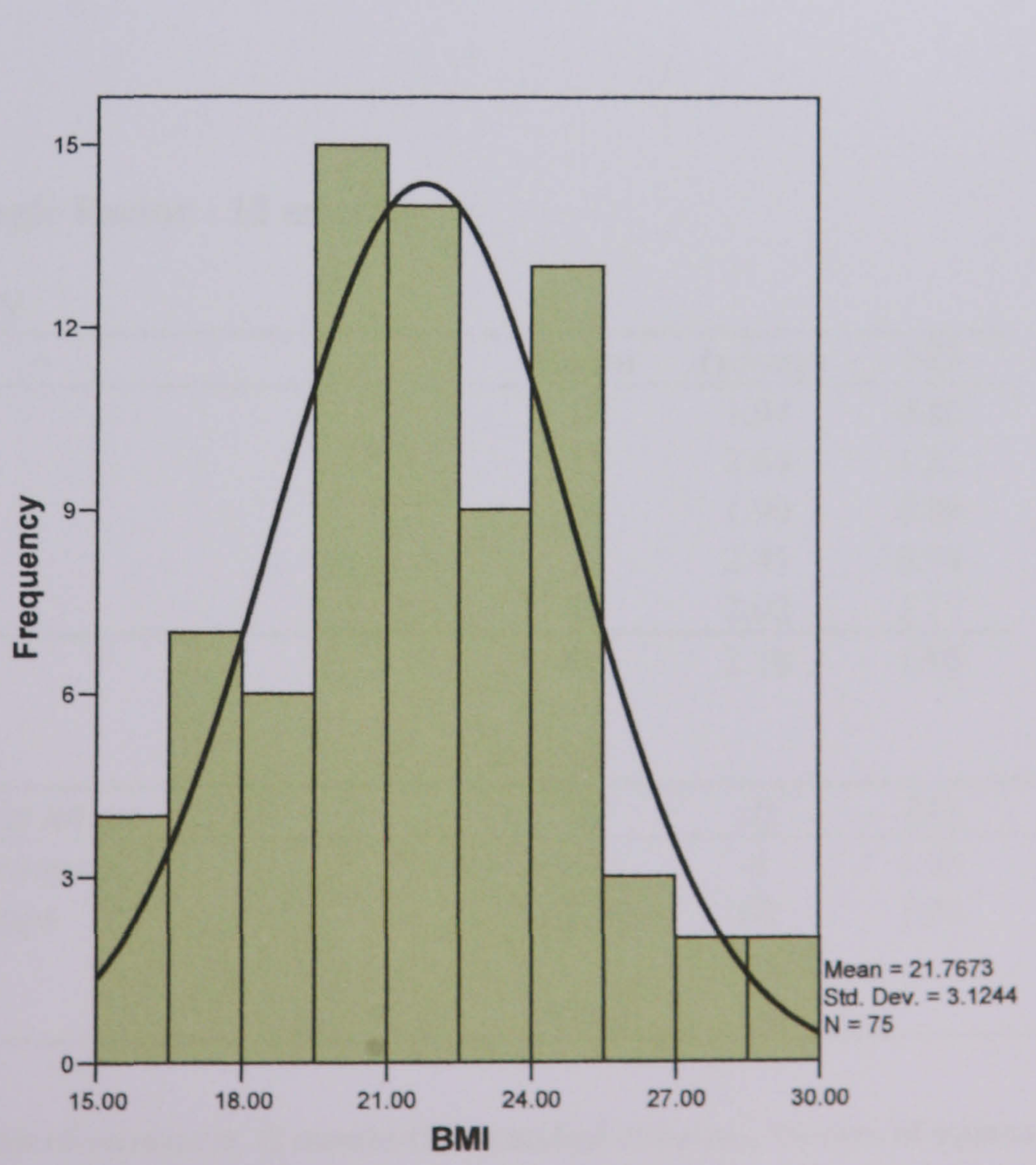
Appendix 19. Distribution of data



Forced expiratory volume in one second (FEV_1) in litres (The black line demonstrates a normal curve).



Age in years (The black line demonstrates a normal curve).



Body mass index (BMI) in kilograms/metres^2 (The black line demonstrates a normal curve).

Appendix 20. One-way analysis of variance (ANOVA)

Anova: Single Factor - 0 months

SUMMARY

Groups	*Count*	*Average*	*SD*
ACBT-0	13	2.01	0.82
AD-0	13	2.68	1.29
Cornet-0	14	1.93	0.87
Flutter-0	12	2.46	0.97
PEP-0	13	2.17	1.14
Overall	65	2.24	1.04

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*
Between Groups	5.22	4	1.30	1.23	0.31
Within Groups	63.89	60	1.06		
Total	69.10	64			

One way analysis of variance at 0 months (SD=standard deviation, SS=sum of squares, df=degrees of freedom, MS=mean of squares, F=variance).

Anova: Single Factor - 12 months

SUMMARY

Groups	*Count*	*Average*	*SD*
ACBT-12	13	1.94	0.80
AD-12	13	2.64	1.22
Cornet-12	14	1.90	0.89
Flutter-12	12	2.43	0.94
PEP-12	13	2.02	1.17
Overall	65	2.18	1.03

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*
Between Groups	5.72	4	1.43	1.39	0.25
Within Groups	61.90	60	1.03		
Total	67.62	64			

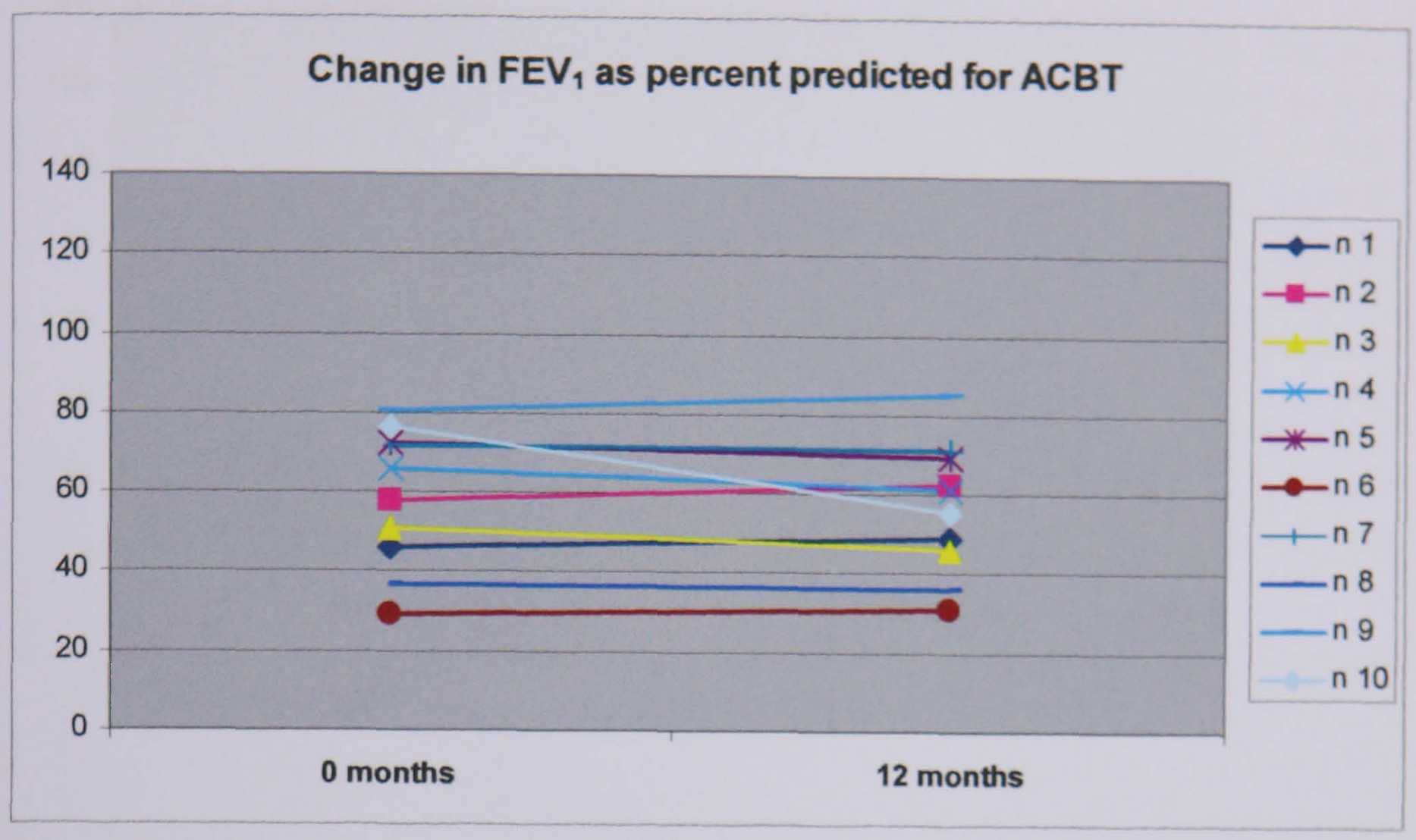
One way analysis of variance at 12 months (SD=standard deviation, SS=sum of squares, df=degrees of freedom, MS=mean of squares, F=variance).

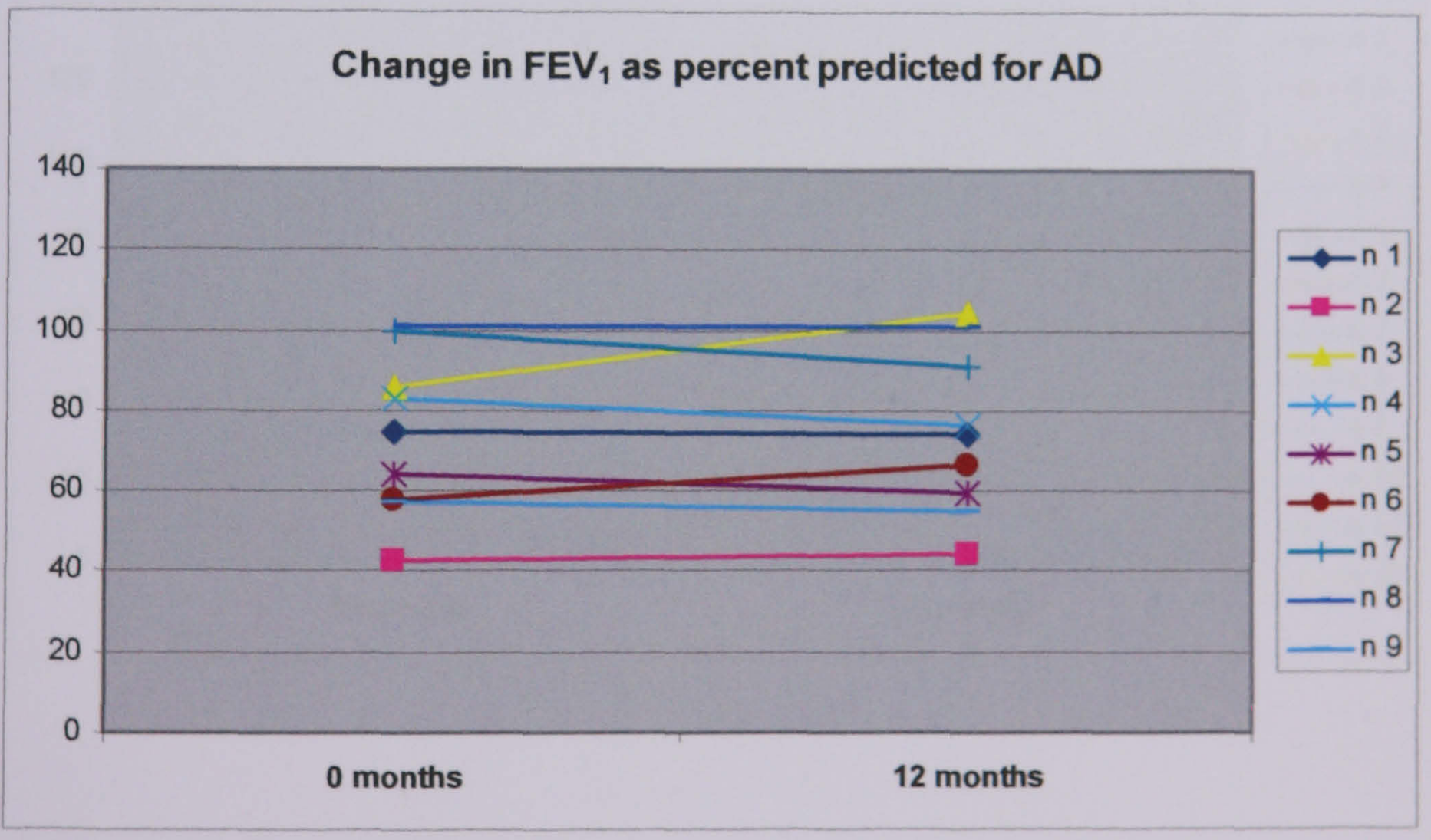
Appendix 21. Lung function

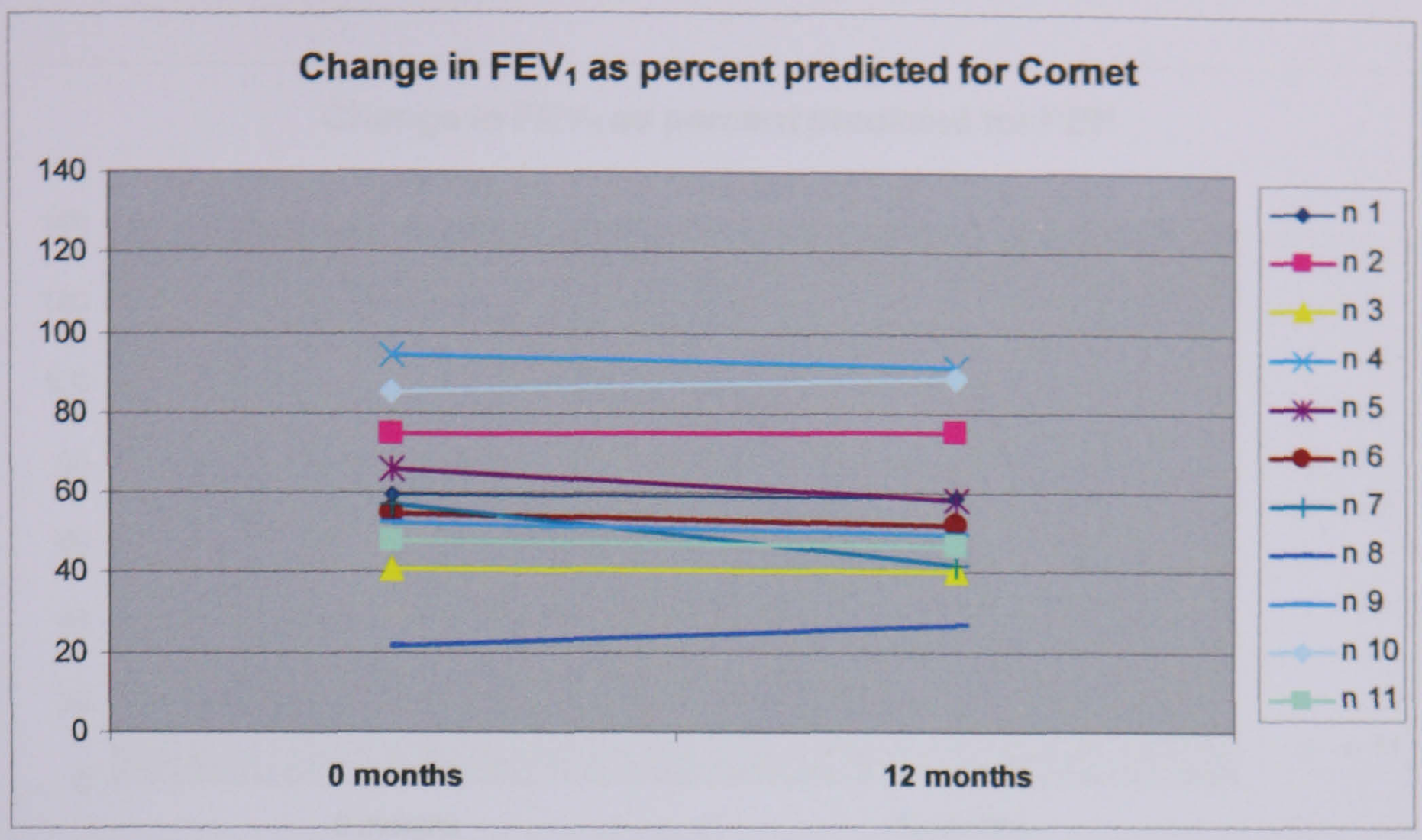
Lung Function (litres) Mean (SD)															
	ACBT			AD			Cornet			Flutter			PEP		
	0 months	6 months	12 months	0 months	6 months	12 months	0 months	6 months	12 months	0 months	6 months	12 months	0 months	6 months	12 months
	n=15	n=11	n=10	n=15	n=6	n=9	n=15	n=11	n=11	n=15	n=13	n=12	n=15	n=13	n=11
FEV_1	1.97 (0.77)	1.92 (0.68)	2.14 (0.81)	2.55 (1.28)	2.54 (0.97)	2.99 (1.07)	1.91 (0.84)	1.89 (0.89)	2.09 (0.85)	2.36 (0.89)	2.37 (0.89)	2.43 (0.94)	2.12 (1.06)	2.14 (1.10)	2.23 (1.15)
FVC	3.59 (1.14)	3.43 (1.18)	3.84 (1.27)	3.78 (1.49)	3.68 (1.06)	4.21 (1.25)	3.04 (1.15)	3.14 (1.30)	3.43 (1.19)	3.63 (1.04)	3.52 (1.13)	3.69 (0.94)	3.37 (1.10)	3.52 (1.14)	3.53 (1.16)
RV % TLC	48.12 (10.36)	48.02 (9.70)	45.28 (10.24)	41.52 (14.56)	42.36 (13.83)	36.87 (10.07)	46.68 (13.52)	47.75 (11.87)	44.72 (11.96)	44.19 (11.03)	43.01 (13.89)	43.19 (11.22)	45.77 (13.24)	45.82 (13.91)	46.74 (16.37)
Median (interquartile range)															
MEF_{25}	0.24 (0.16,0.44)	0.28 (0.21,0.38)	0.28 (0.21,0.52)	0.49 (0.18,0.84)	0.50 (0.39,0.52)	0.53 (0.47,1.08)	0.27 (0.16,0.46)	0.29 (0.15,0.46)	0.33 (0.26,0.48)	0.36 (0.19,0.74)	0.41 (0.22,0.69)	0.39 (0.20,0.70)	0.23 (0.11,0.72)	0.34 (0.15,0.60)	0.27 (0.17,0.63)

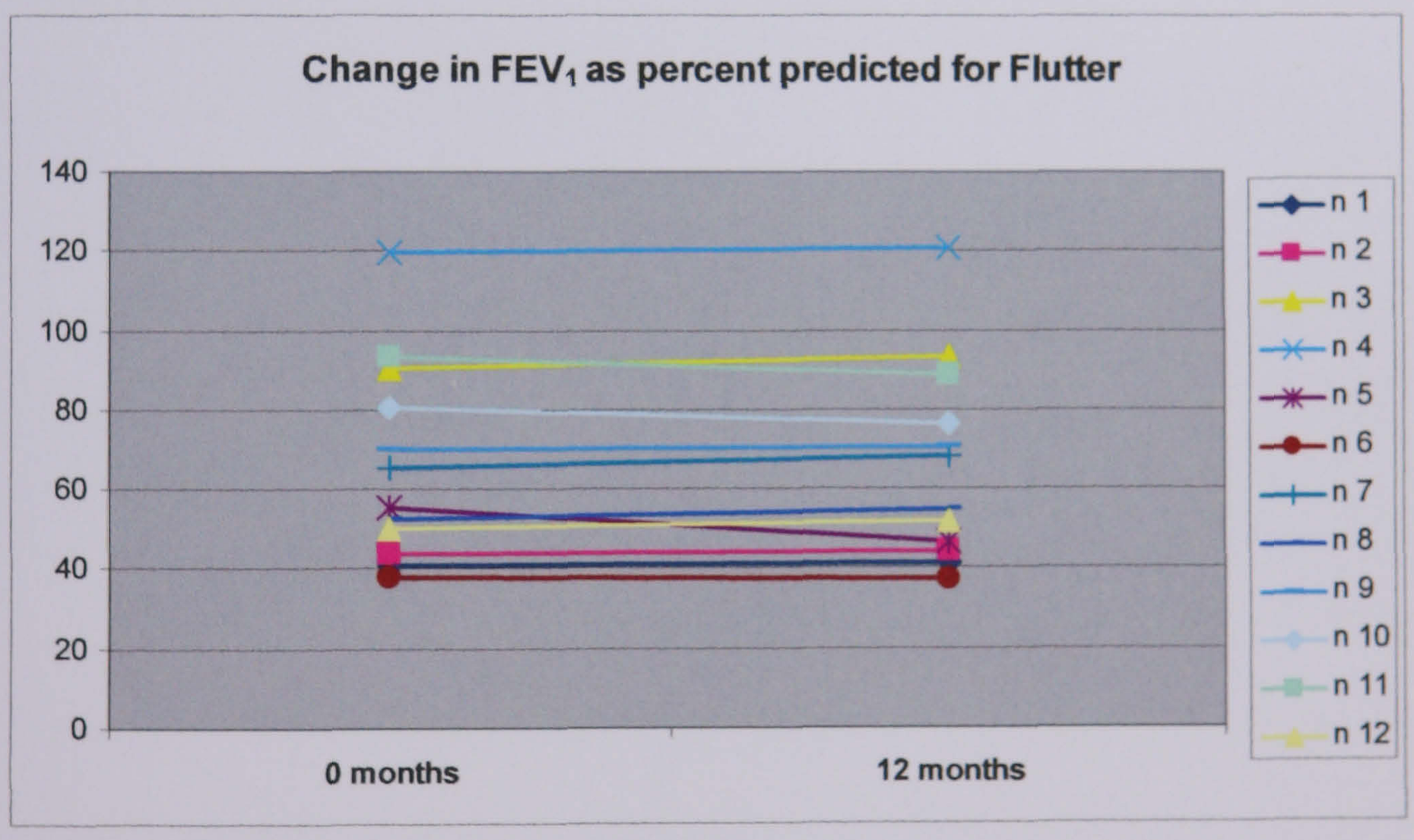
Lung function values for forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), residual volume as a percent of total lung capacity (RV%TLC), and maximal expiratory flow at 25% of forced vital capacity (MEF_{25}) for subjects who remained on the study (n= number of subjects).

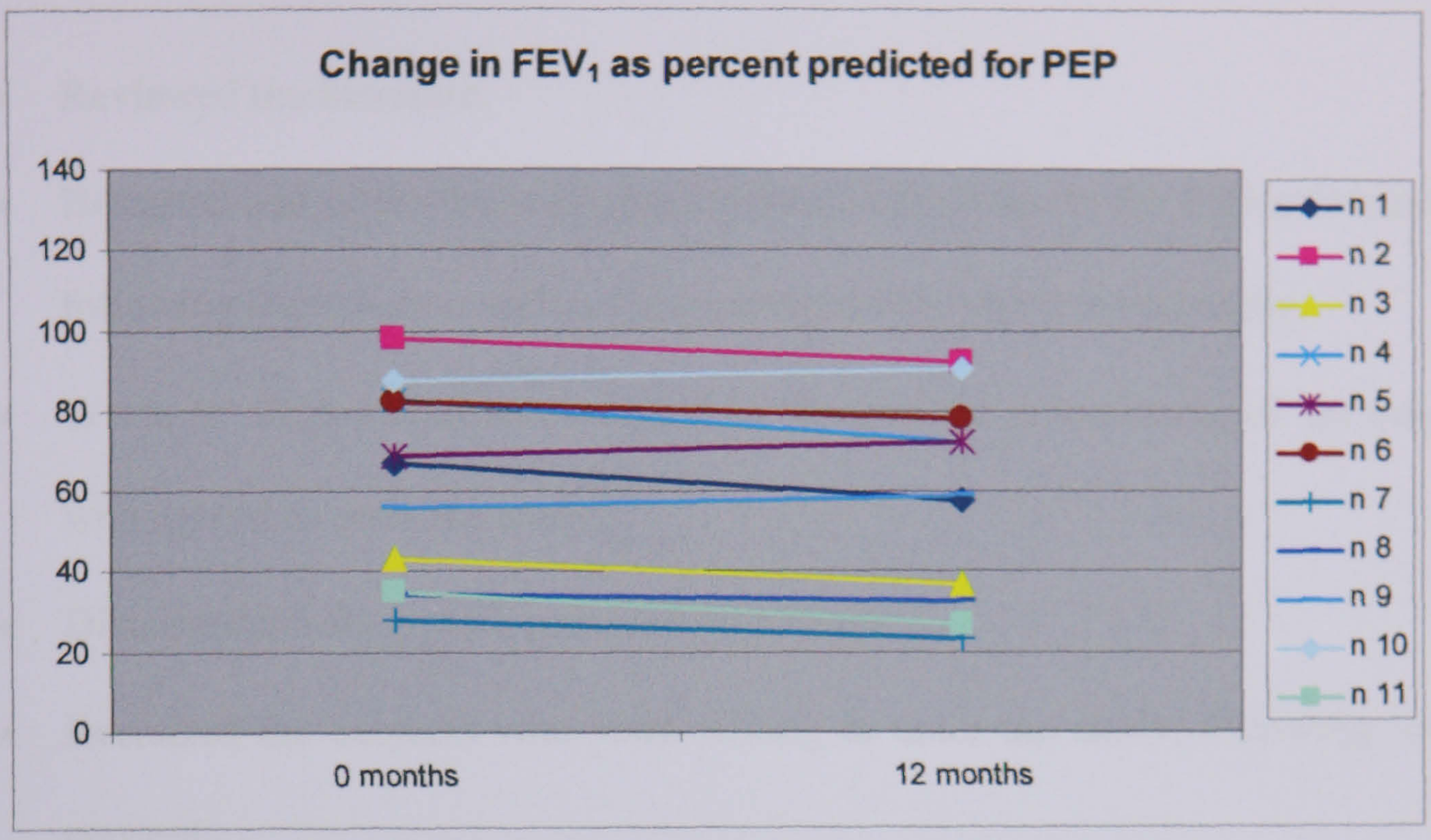
Appendix 22. Individual changes in FEV_1 as percent predicted






Change in FEV1 as percent predicted for Cornet
140
120
100
80
60
40
20
0
0 months
12 months
n 1
n 2
n 3
n 4
n 5
n 6
n 7
n 8
n 9
n 10
n 11


Change in FEV1 as percent predicted for Flutter
140
120
100
80
60
40
20
0
0 months
12 months
n 1
n 2
n 3
n 4
n 5
n 6
n 7
n 8
n 9
n 10
n 11
n 12


Change in FEV1 as percent predicted for PEP
140
120
100
80
60
40
20
0
0 months
12 months
n 1
n 2
n 3
n 4
n 5
n 6
n 7
n 8
n 9
n 10
n 11

Appendix 23. Author's personal contribution to this study

- Reviewed the literature.
- Designed and wrote the study protocol for submission to the Ethics Committee, following consultation with colleagues nationally and internationally.
- Wrote to all potential subjects and to the general practitioners of the subjects who agreed to enter the study.
- Discussed the study with prospective subjects.
- Recruited the subjects who were willing to enter the study, following written consent.
- Documented entry to the study in the subject's medical notes and with the Ethics Committee.
- Assessed and instructed the subjects in their allocated treatment regimens, initially and at monthly intervals as possible (supporting the training of the patients on the autogenic drainage arm together with experts in that technique).
- Undertook the monthly lung function spirometric measurements, to objectively monitor the subject's clinical state.
- Undertook the modified shuttle tests with computerised recordings of oxygen saturation and supervised completion of the modified Borg scale.
- Interviewed the subjects using the Chronic Respiratory Questionnaire
- Supervised completion of the Short Form-36 questionnaire.
- Made contact with the medical staff on a subject's behalf, if this was indicated, or contact with other health professionals, for example clinical specialist nurse and social worker.

- Liaised with the proponents of the regimens and organised their visits to Royal Brompton Hospital.
- Input all the data from the study for analysis.
- Undertook the statistical analysis using one-way analysis of variance (ANOVA), Excel and SPSS, but had professional statistical help from Mr Mohammed Khan (Statistician at Royal Brompton Hospital) for the analysis using the mixed model analysis of variance and the two-sample test for equality of proportions with continuity corrections; and from Mrs Jackie Turner (Statistician) for the initial power calculation.
- Wrote the thesis.

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