

**THE RELATIONSHIP BETWEEN LUNG  
MECHANICS AND BREATHLESSNESS  
IN CHRONIC OBSTRUCTIVE  
PULMONARY DISEASE**

**Thesis submitted in accordance with the requirements of the  
University of Leicester for the degree of Doctor of Medicine  
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## SUMMARY

Breathlessness and limited exercise tolerance are the principal symptoms of COPD. Bronchodilator therapy is directed towards the relief of these disabling symptoms but little is known of the mechanism of relief of dyspnoea or which tests best predict symptomatic benefit from bronchodilator. This thesis examines the appropriateness of a range of radiological and physiological tests in assessing disease severity and the symptomatic benefit derived from bronchodilators and examines the physiological mechanisms which result in reduced dyspnoea following their use.

The estimation of lung volume radiographically was disappointing and was only comparable with other methods for group data. Agreement within individual patients was poor. My data suggests that radiological measures of lung volume are unsuitable for individual patient studies but it may still be useful in retrospective epidemiological studies where other lung volume data is not available.

Inhaled oxitropium bromide and nebulised salbutamol both improved 6 minute walking distance, the improvement in exercise capacity being independent of improvements in FEV1 or FVC. Resting breathlessness was significantly improved by both oxitropium and salbutamol, whilst end of walk breathlessness was improved following oxitropium. Both these measures of improvement were independent of spirometric improvement. However increases in peak inspiratory flow rate after oxitropium bromide correlated significantly with improvements in end of walk breathlessness.

Improvements in breathlessness and walking distance were not explained by reductions in lung volume measured either by helium dilution or body plethysmography. Trapped gas volume proved to be an unreliable measurement and had no value in the prediction of functional benefit from bronchodilator.

Large falls in resting airways resistance occurred in these COPD patients following oxitropium bromide. The falls in airways resistance occurred

independently of improvements in spirometry but were not quantitatively related to improvements in either breathlessness or 6 minute walking distance.

Mouth occlusion pressure was not a correlate of resting breathlessness neither did changes in P0.1 correlate with reductions in breathlessness. The presence of severe airflow obstruction and PEEPi make the measurement of mouth occlusion pressure suspect in these patients.

Oxitropium bromide caused a small fall in resting oxygen saturation, salbutamol had no effect on resting saturation. Corridor walking exercise produced brisk falls in oxygen saturation, but the severity of desaturation was unaffected by the bronchodilator. Recovery from desaturation at the end of the walk was rapid.

Histamine challenge increased breathlessness but alterations in levels of breathlessness were not correlated with the increases in end expiratory lung volume provoked by the challenge.

Oxitropium bromide reduced positive end expiratory pressure (PEEPi), respiratory accessory muscle activity and reduced pleural pressure swings during hypoxia and hypercapnia stimulated breathing. Thus the efficiency of ventilation was improved by their inhaled bronchodilator. There was no difference in the rate of change of breathlessness with increasing ventilation between isocapnic hypoxaemic and progressive hypercapnic stimulated breathing.

In conclusion an anticholinergic bronchodilator can improve exercise capacity and breathlessness, independent of changes in conventional lung function tests or alterations in oxygen saturation. Alterations in these measurements which relate to dynamic changes occurring during respiration such as PEEPi, accessory muscle activity and pleural pressure swings may be more useful in assessing the response to bronchodilator drugs.

## **DECLARATION**

This thesis is the result of my own work. The material contained in the thesis has not been presented either wholly or in part for any other degree or qualification

The research work was carried out in the Respiratory Function Laboratory, Aintree Chest Centre, Fazakerley Hospital Liverpool.

The author performed all the experimental work except the helium dilution lung volume measurements which were performed by the technicians of the Respiratory Function Laboratory.

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## Glossary of terms and abbreviations

|          |                                                            |
|----------|------------------------------------------------------------|
| COPD     | Chronic obstructive pulmonary disease                      |
| EMG      | Electromyogram                                             |
| Fb       | Breathing frequency                                        |
| F25      | Flow after 25% of vital capacity exhaled                   |
| F50      | Flow after 50% of vital capacity exhaled                   |
| F75      | Flow after 75% of vital capacity exhaled                   |
| FEF25-75 | Mean expiratory flow between 25% and 75% of vital capacity |
| FEV1     | Forced expiratory volume in 1 second                       |
| FRC      | Functional residual capacity                               |
| FVC      | Forced vital capacity                                      |
| IC       | Inspiratory capacity                                       |
| IES      | Inspiratory effort sensation                               |
| IPPBT    | Intermittent positive pressure breathing trial             |
| MVV      | Maximal voluntary ventilation                              |
| Pdi      | Transdiaphragmatic pressure                                |
| Pdimax   | Maximum transdiaphragmatic pressure                        |
| PEEPi    | Intrinsic positive end expiratory pressure                 |
| Pemax    | Maximum expiratory pressure                                |
| Pes      | Oesophageal pressure                                       |
| Pimax    | Maximum inspiratory pressure                               |
| Ppl      | Pleural pressure                                           |
| Te       | Expiratory time                                            |
| TGV      | Thoracic gas volume                                        |
| Ti       | Inspiratory time                                           |
| Trs      | Time constant for respiratory system emptying              |
| TTI      | Tension time index                                         |
| Ttot     | Respiratory cycle duration                                 |

|     |                             |
|-----|-----------------------------|
| V/Q | Ventilation perfusion ratio |
| Vc  | Vital capacity              |
| Ve  | Expired minute ventilation  |
| Vt  | Tidal volume                |
| VTG | Trapped gas volume          |

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## Introduction

Breathlessness and exercise limitation are the principal symptoms of chronic obstructive pulmonary disease (COPD), and their relief is the aim of treatment of this condition for which only symptomatic treatment is available.

This thesis examines the effect of bronchodilator drugs on lung mechanics, exercise tolerance and breathlessness in patients with stable COPD and explores the relationships between these different but related processes.

Chronic airflow limitation is the result of a range of pathological processes. Many attempts have been made to define asthma, emphysema and chronic bronchitis in terms of specific pathological processes which lead to an increase in resistance to airflow. In 1959 the Ciba Symposium defined emphysema in terms of morbid anatomical appearance ie the permanent enlargement of the respiratory passages and air spaces distal to the terminal bronchiole, a definition which is now generally accepted though modified to include associated alveolar wall destruction. Asthma was defined functionally in terms of reversibility of airflow obstruction a principle which is widely accepted though the degree of bronchodilator reversibility necessary to define airflow obstruction as asthmatic has not been agreed. Furthermore, the classification of those asthmatic patients who develop persistent irreversible obstruction is difficult. Nor is it known if the functional consequences of irreversible chronic asthma differ from those of non-asthmatic chronic irreversible airflow obstruction. The MRC bronchitis research committee of 1965 defined chronic bronchitis and classified it into three categories:

- 1) Simple chronic bronchitis with chronic or recurrent mucus hypersecretion sufficient to cause expectoration.

2) Chronic or recurrent muco-purulent bronchitis where hypersecretion is complicated by episodes of infection with muco-purulent secretions.

3) Chronic obstructive bronchitis with hypersecretion of mucus associated with widespread persistent narrowing of the intra pulmonary airways.

Unfortunately defining 3 grades implies a progression from 1 to 3 in the natural history of development of airflow obstruction. This did not prove to be the case (expectoration alone is not causally related to the development of airflow obstruction (Fletcher 1984)).

The clinical relevance and/or usefulness of classifying patients into such categories is limited as is the attempt to label the pathology as emphysema, chronic obstructive bronchitis or chronic irreversible asthma. Emphysema and chronic bronchitis often co-exist in the same patient (Thurlbeck 1990) and it may be more appropriate to group all patients together under the label chronic obstructive pulmonary disease (COPD). This may be defined as a process characterised by the presence of chronic bronchitis or emphysema that may lead to the development of airways obstruction; airways obstruction need not be present at all stages of the process; the airways obstruction may be partially reversible (Snider 1989). These abnormalities in turn lead to abnormalities of chest wall musculature and to problems with gas exchange.

### **Physiological correlates of the pathological features of COPD**

As suggested above the pulmonary lesions associated with COPD are often multiple and usually inter-related. The commonest cause is the chronic inhalation of tobacco smoke.

Studies of the pathology of COPD have generally been of two types, retrospective where the interval between pulmonary function testing and

post mortem histology was often long, and prospective where histological material has been obtained from patients undergoing lung resection, usually for neoplasia. In these patients the interval between pulmonary function testing and histology is short but the group is self selecting for those with only a modest degree of impairment to lung function (those with the more severe disease are not considered for resection of a lung tumour). The most complete prospective study which was not constrained by the limitations of surgical suitability was obtained from those patients who died during the course of the North American National Institutes of Health intermittent positive pressure breathing trial (IPPBT). Nagai et al (1985) examined the relationship between indices of airflow obstruction and their pathological correlates. Forty eight patients died during the course of this trial and came to post mortem. These patients had moderate to severe airflow obstruction (FEV1 11% to 57% predicted, mean 30.9%, FEV1/ FVC 37.5% (11% to 57%).

### Lesions of the bronchi

#### A) Mucous Gland Enlargement

Nagai (1985) found mucous glands were increased in size but normal in number in the central airways. Goblet cell metaplasia within the bronchiolar walls was related to dyspnoea and to %predicted FEV1 and airways resistance. Goblet cell size was inversely related to bronchodilator reversibility and to % predicted FEV1 and airways resistance. In contrast Cosio (1978) in a group of patients whose lungs were resected because of carcinoma found no relationship between goblet cell numbers or distribution and any measure of lung function.

#### B) Bronchial Smooth Muscle Hyperplasia

Smooth muscle hyperplasia in COPD was reported by Nagai et al (1985). The degree of muscle hyperplasia was unrelated to the degree of airflow obstruction nor was it related to bronchial reactivity or reversibility of airflow obstruction assessed by improvement in FEV1 following 250mcg inhaled isoproterenol or by variability in spirometric indices.

#### C) Cartilage Atrophy

Atrophy of cartilage was not a feature of the patients studied in the IPPB trial. Meisel (1968) reports bronchial atrophy in association with expiratory airway collapse, and Mullen (1985) in a study of surgically resected specimens found cartilage atrophy was related to airflow obstruction.

#### D) Bronchial Inflammation

Inflammation of the bronchi was not consistent in the IPPB trial, nor in the study by Mullen (1985). Importantly there was no relationship between the degree of inflammation and non specific airway reactivity to histamine or to bronchodilator response. Nor was bronchial eosinophilia positively associated with an increase in bronchodilator response (in fact a negative association was found).

#### E) Bronchial Wall Thickening

McKensie (1969) found a doubling of bronchial wall thickness in COPD in a group of coal miners with COPD, but this was not measured in the IPPBT. Moreno (1986) in a theoretical review article has described the relationship between Raw and external bronchial diameter and bronchial wall cross sectional area. A thickened bronchial wall will result in a larger

proportion of the external cross sectional area of the bronchus being taken up by bronchial wall and since bronchial wall is incompressible a given reduction in cross sectional area will result in a larger reduction in luminal diameter in a thick walled bronchus than a thin walled one. Poiseulles law can be used to calculate the change in resistance in a single airway; resistance to airflow increases exponentially as external diameter decreases and as bronchial wall area occupies an increasing proportion of the total cross sectional area of the bronchus. Freedman (1972) and Pare (1991) have proposed increased airway wall thickness as a mechanism for the increased bronchial reactivity seen in asthma and COPD.

### The small airways

#### A) Bronchiolar inflammation and narrowing

Several studies have demonstrated inflammation of the bronchioles in COPD (Nagai (1985), Berend (1981), Cosio(1978)). Berend et al showed a relationship between bronchiolar narrowing and FEV1, FEF25-75 and closing volume. Salmon (1982) described a relationship between peripheral airway diameter and the phase III slope of the single breath nitrogen washout while Petty (1982) described a negative correlation between bronchiolar internal diameter and closing volume and a positive correlation between small airway internal diameter and FEV1.

#### B) Fibrosis Of Bronchiolar Walls

Nagai et al (1985) found the presence of bronchiolar wall fibrosis correlated with higher expiratory flows, higher oxygen tensions a lower PCO2 and less breathlessness. Patients with bronchiolar wall fibrosis were also less hyperinflated. They postulate that this beneficial association may be due to stabilisation of the bronchiolar walls making them less



liable to deformation during expiration and effort dependent airway collapse.

#### C) Increased Bronchiolar Smooth Muscle.

The effect of increased smooth muscle is controversial. Cosio (1978) and Nagai (1985) have demonstrated an increase in small airway smooth muscle associated with improved clinical status and a high FEV1. The reason again was presumed to be stabilisation of the bronchiolar wall and prevention of collapse. Whereas Cosio (1985) in a subsequent study found the converse, namely increased smooth muscle being associated with a lower FEV1. Another study by Petty (1982) in patients with mild COPD found no association between FEV1 and smooth muscle dimensions.

#### D) Loss Of Alveolar Attachments

Loss of the supporting structure of the bronchioles and loss of radial traction upon them, as seen in emphysema, predisposes to premature airway collapse. Hale et al (1984) found emphysema and air space enlargement correlated strongly negatively with percent predicted FEV1 ( $r = -0.74$ ). Saetta (1985) found loss of alveolar attachments to correlate with mild chronic airflow obstruction, and Petty (1986) found a correlation between loss of elastic recoil and the loss of these attachments. Nagai (1985) found significant correlations between histological emphysema and an increased residual volume, and the same group (West 1987) found the degree of emphysema was correlated with plethysmographic TLC. Interestingly Nagai (1985) found the severity of emphysema was not a correlate of breathlessness.

## THE EFFECT OF AIRFLOW LIMITATION ON THE STRUCTURE AND FUNCTION OF THE THORACIC MUSCULATURE

In order to better understand the mechanisms of dyspnoea in COPD it is useful to consider the consequences of increased resistance to airflow on the thoracic musculature.

The primary effect of airflow limitation and an increased airways resistance is hyperinflation of the thorax. This places the inspiratory muscles at a mechanical disadvantage.

### Structure

Several pathological studies have examined the respiratory muscles in COPD though the results are not conclusive. Thurlbeck (1990) found that diaphragmatic weight (and body weight) were reduced even in mild asymptomatic emphysema and that the decline in diaphragmatic weight was progressive with increasing severity of emphysema. In contrast Arora (1982) found no difference between diaphragmatic dimensions in COPD patients and in age and sex matched controls. Ishikawa (1973) found the diaphragm was hypertrophied in COPD compared to matched controls.

Studies in hamsters with elastase induced emphysema (Farkas 1983, Kelsen 1983) have suggested that a change in fibre type occurs in the diaphragm, with fast fibre atrophy and slow fibre hypertrophy. However it is not known whether similar changes occur in the non-experimental emphysema in humans. Other work by the same author (Farkas 1983) has found that diaphragmatic muscle sarcomere absorption occurs in experimentally induced emphysema suggesting that in COPD some compensation may occur in response to persistent hyperinflation in order that diaphragmatic length tension

relationships may be maintained. Longitudinal studies examining diaphragmatic structure in developing COPD have not been attempted in man.

### Function

The efficiency of the respiratory muscles is determined by their length tension relationships and the geometry of their action. Hyperinflation reduces the efficiency of the diaphragm. It starts from a shorter initial length and works at a mechanical disadvantage because of its smaller zone of apposition with the chest wall. The decreased radius of curvature also results in more medial orientation of muscle fibres with consequent loss of pressure generating ability (Macklem 1983). The efficiency of the diaphragm is further reduced because an increased force must be generated to produce airflow as a consequence of increased airways resistance. Furthermore effort is wasted in attempting to overcome airway collapse on expiration. In this situation increased intrathoracic pressure only results in increased airway collapse. (Sharp 1968)

### Respiratory Muscle strength in COPD

Inspiratory muscle strength is reduced in COPD (Rochester 1979), a finding which may be attributed to hyperinflation. However further work by the same author (Rochester 1985) has suggested that expiratory muscle strength is also reduced in COPD, a finding which cannot be explained by hyperinflation. In a study of 32 patients and 22 normal subjects the reduction in  $P_i$  Max in those patients whose  $P_e$  Max was normal could be almost entirely explained by the effect of diaphragmatic shortening when compared to the normal controls. Whereas in those patients who had a reduced  $P_e$  Max only part of the reduction in  $P_i$  Max could be explained by diaphragmatic shortening. The authors postulate a generalised respiratory muscle weakness in some patients with COPD. Several possible causes for

this global weakness have been identified. Both hypoxia and hypercapnia reduce endurance times during exercise (Criner 1987) and during resistive loaded breathing (Jardim 1981, Juan 1984). Reductions in muscle ATP, phosphocreatine, and a glycogen have also been reported together with malnutrition (Campbell 1980). Weight loss is common in COPD as mentioned above (Thurlbeck 1990) and 20% of patients have a body weight of less than 85% of the ideal for height and build (Tobin 1988).

Ventilatory endurance is reduced in COPD, which may be because of the mechanical disadvantages of hyperinflation. The fraction of MVV which can be sustained is similar to normal subjects, though in absolute terms the values are much reduced. In normal subjects MVV is primarily related to muscle strength whereas in COPD the major determinant is the degree of airflow obstruction although MVV also depends on the pressures which can be generated within the thorax (Aldrich 1982).

### Respiratory Muscle Fatigue

Fatigue of any muscle may be defined as the failure to maintain the required or expected force (Edwards 1981) and occurs in the context of the respiratory system when respiratory muscle endurance is exceeded, ie when the load against which the muscles must contract requires too great an effort for too long.

One consequence of the reduced muscle efficiency through hyperinflation and an increased airways resistance in COPD is that the respiratory muscles are predisposed to increased risk of fatigue. Diaphragmatic fatigue is likely to occur in normal subjects (at least when inspiratory flows are fixed) when the tension time index (TTI) (the product of  $T_i/T_{tot}$  and  $P_{di}/P_{di\max}$ ) of the diaphragm reaches 0.15 (Bellemare 1982). In COPD the tension time index of the diaphragm was [mean(SD)] 0.05(0.04) during resting breathing (about 3

times higher than normal) indicating a low functional reserve and diaphragmatic EMG evidence of fatigue was evident when  $T_i/T_{tot}$  or  $V_t$  were increased increasing the TTI to 0.17 (Bellemare 1983). The occurrence of respiratory muscle fatigue during exercise in COPD is controversial (see below).

#### The control of functional residual capacity in COPD

Functional residual capacity (FRC) is the lung volume at which the elastic recoils of the chest wall and lung are equal in magnitude but opposite in sign. In normal subjects during quiet breathing FRC is determined by static forces. In COPD lung recoil is reduced (Macklem 1963) whereas chest wall compliance has been shown to be normal when complete chest wall relaxation is achieved with neuro muscular blockade (Sharp 1967).

Reductions in lung recoil will explain moderate increases in FRC but larger increases beyond the normal relaxation volume of the chest wall (65 to 70% TLC) requires either a change in the pressure volume characteristics of the chest wall or that FRC is determined by dynamic factors (Martin).

Vinegar (1979) has described a relationship between FRC, tidal volume,  $V_r$  (the relaxation volume of the respiratory system),  $T_e$  and the time constant for respiratory system emptying ( $t_{rs}$ ).

$$FRC - V_R = \frac{V_t}{T_e/t_{rs} - 1}$$

Clearly as  $T_{rs}$  rises or  $T_e$  falls then FRC will rise.  $T_{rs}$  is largely dependent on the passive mechanical properties of the respiratory system.  $T_e$  will fall with the loss of post inspiratory braking which occurs in COPD (Citterio 1981). In COPD the time constants of the respiratory system are prolonged. Under these circumstances inspiratory muscle activity is often initiated before the end of the preceding expiration (Morris 1990)

and before the respiratory system elastic recoil equilibrium is reached (resulting in intrinsic PEEP). If expiratory time is shortened relative to  $T_{rs}$  then FRC will rise. Thus the elevation of FRC seen in obstructive lung disease is both neurally mediated through muscle activation and a consequence of prolonged respiratory system time constants. The active control of FRC may represent a reflex adjustment to increase the efficiency of ventilation or to achieve a breathing pattern which results in least dyspnoea. Alternatively the elevation of FRC may be an inevitable consequence of increased lung emptying time.

### The sensation of dyspnoea

The Handbook of Physiology describes dyspnoea as the unpleasant sensation of laboured breathing which may vary in intensity from awareness of difficulty breathing during exertion to incapacitating distress at rest (Rebuck and Slutsky). Dyspnoea may occur when breathing is hindered or when ventilation is excessive (Cambell and Howell 1963). Hindered breathing is an uncommon sensation in normal individuals except when wearing a tight garment or face mask whereas excessive ventilation is a well recognised feature of exertion. Campbell and Guz (1981) describe 4 elemental sensations which either singularly or in combination underlie the sensation of breathlessness:

- 1) Tightness
- 2) Excessive ventilation
- 3) Excessive frequency of ventilation
- 4) Difficulty in the act of breathing

Other authors have suggested that the sensation may be made up of more discreet sensations. Simon et al describe 9 different sensations which may be distinguished by normal volunteers all of which describe different aspects of the sensation of breathlessness (Simon 1989). More recently the same group (Simon 1990) and others (Elliott et al 1991) have related these sensations to patients with dyspnoea due to a variety of cardiorespiratory and neuromuscular conditions. The descriptors chosen by patients with COPD which best described their dyspnoea were 'work' and 'hunger'. Interestingly these descriptors were distinct from those used to describe the dyspnoea of asthma which were 'exhalation', 'work' and 'tight' despite airflow limitation being the functional consequence of both conditions.

The authors suggest this may be a consequence of stimulation of airway irritant receptors in asthma and not in COPD modulating the symptom of

dyspnoea however another possibility is the differing duration of loading in the 2 conditions, chronic in COPD and intermittent in asthma.

The breathlessness of chronic obstructive pulmonary disease is probably multi-factorial. It is possible that the attenuation of dyspnoea which results from altering lung mechanics is qualitatively different from the relief of dyspnoea obtained from oxygen administration though this has not been studied.

Campbell and Howell in 1964 devised a unifying theory of the mechanism of dyspnoea. Their concept of length tension inappropriateness is still attractive today. Modifications of the theory have been suggested. Leblanc et al (1986) suggested that the unifying concept would be better expressed as effort tension inappropriateness.

The act of breathing requires nervous activation of the respiratory muscles which in turn requires central nervous system input. Anything which disturbs the relationship between the effort required to breath, (neural drive) and the response of the respiratory muscles (ventilation) will result in dyspnoea. Experience suggests the level of effort or activation required to produce a given level of ventilation and anything which disturbs the expected motor output from a given neural input may result in dyspnoea. The disturbance may be due to reduced pump activity eg breath holding, hypoventilation or neuromuscular disorders, or any respiratory disorder which reduces the efficiency of the respiratory pump eg hyperinflation, increased airways resistance, muscle fatigue or impaired gas exchange.

Supporting experimental evidence for the theory of Campbell and Howell has been obtained from many experimental models, both in normal man and in subjects with respiratory disease. These experiments suggest an important role for chest wall proprioception in the perception of breathlessness.



### Breathholding Experiments

Breathholding has been used extensively in the study of the mechanisms of breathlessness since the description of the experiment by Hill and Flack in 1908. In this experiment the breath was held for as long as possible until an intolerable urge to breathe was reached. Hill noted that the breath hold time varied widely between individuals, and also within the same individual under differing conditions of relaxation. Breath holding experiments have the advantage that quantitative assessment of sensation is avoided. The validity of this experimental model is based on the assumption that the sensation at break point of a breathhold represents an extreme form of dyspnoea, an assumption which may be questioned.

Early breath holding experiments (Fowler 1954) showed that breathing of a high CO<sub>2</sub> low O<sub>2</sub> gas mixture at break point relieved the unpleasant sensation associated with breath holding. This suggested that chest wall displacement played a more important role in the genesis of the sensation of breathlessness during a breath hold than did disturbed blood gases. Similarly Rigg (1974) demonstrated that a breathhold may be prolonged by an isovolume manoeuvre at break point. Campbell et al (1967,1969) have shown that neuromuscular blockade with curare abolishes the unpleasant sensation associated with breathholding, while Kobayasi (1984) has demonstrated that greater derangement of blood gases are tolerated during CO<sub>2</sub> rebreathing experiments than during breathholding. Whitelaw et al (1987) have emphasised the importance of the chest wall and diaphragmatic musculature by demonstrating that the rhythmic diaphragmatic contractions which occur close to break point of a breath hold are delayed in onset by breathholding near to TLC.

## Exercise

Exercise causes breathlessness in both normal individuals and in patients with cardiopulmonary disease. The difference between them is the degree of exertion required to produce dyspnoea, and possibly the sensation itself (Howell 1966). Dyspnoea increases progressively with increasing work load, and several studies have examined the relationship between perceived breathlessness and respiratory mechanics. Leblanc et al (1986) demonstrated that breathlessness was related to fractional respiratory variables (the dynamic variable measured during tidal breathing expressed as a percentage of their maximal static values ie  $P_{pi}/P_{imax}$ ,  $V_t/VC$ ,  $T_i/T_{tot}$  and  $F_b$ ). They found that a multiple regression analysis including all these variables explained 83% of the variance of the sensation of breathlessness during increasing work load exercise. El-Manshawi et al (1986) from the same group also found relationships between breathlessness and  $P_{es}$ , inspiratory flow, breathing frequency and  $T_i/T_{tot}$ . These variables explained a similar variance to the work by Leblanc et al.

Earlier authors (McIlroy and Christie 1954) studying patients with emphysema felt that the work of breathing was an important factor in the genesis of dyspnoea. This construct will not explain the breathlessness associated with muscle weakness. Neither will the construct of Leblanc explain the dyspnoea associated with breathholding or of voluntary hypoventilation (Schwarzstein 1989). These studies (Leblanc 1986, El-Manshawi 1986) suggest that breathlessness on exertion is related to mechanical factors, and that proprioceptive input from the chest wall and diaphragm is important. However breathlessness may be modified by alterations in blood gas tensions. Lane (1987) examined the role of arterial desaturation during exercise on the sensation of breathlessness in COPD. He found that supplemental oxygen sufficient to prevent hypoxaemia

during exercise reduced breathlessness independent of changes in ventilation. Data from Swinburn et al (1991) conflicts with these findings, their study showed that reductions in breathlessness following supplemental oxygen were proportional to reductions in ventilation. Chonan (1990) has suggested that hypercapnia per se may heighten the sensation of dyspnoea.

The sensation of breathlessness may be modified by other factors, Schwarzstein (1987) has shown that cold air blown against the face reduces breathlessness during loaded breathing whereas air blown on the leg had no effect. They postulate that trigeminal nerve stimulation modulates breathlessness in some way. Graham et al (1990) have reported similar reductions in breathlessness in patients with COPD breathing cold air from a mouthpiece suggesting the glossopharyngeal nerve may be responsible. Manning (1991) showed that chest wall vibration reduced the sensation of breathlessness during hypercapnia and resistive loading but had no effect on levels of ventilation again suggesting that chest wall proprioception is important in the sensation of dyspnoea.

#### The effect of central processing on the perception of breathlessness

No simple physiological mechanism can account for the varied perception of dyspnoea between individuals. Respiratory sensations are not uni-dimensional and are subject to affective dimensions, these are particularly prominent when breathlessness begins to impose an increasing restriction on daily activity. In patients with severe COPD with seemingly similar degrees of airflow obstruction there may be a wide variation in the perception of breathlessness. Pink and puffing patients are apparently more breathless than blue and bloating patients who have similar degrees of airflow obstruction, the reason for the difference may be the degree to which the hypercapnic ventilatory response is preserved. Similarly patients in whom

dyspnoea appears to be disproportionate to the degree of airflow obstruction appear to be more likely to suffer from depressive illness, anxiety and hysterical reaction than stoical individuals in whom dyspnoea is a less prominent symptom (Burns 1969)

### Breathlessness in COPD

COPD results in many changes in the respiratory system which may result singly or in combination in dyspnoea

#### 1) Increased minute ventilation

Inefficient gas exchange in COPD due to ventilation (V) perfusion (Q) mismatch (high V:Q ratios acting as a dead space and low V:Q ratios acting as shunts) results in an elevated resting minute ventilation which represents a higher proportion of the total ventilatory reserve than in normal subjects. Mueller (1970) showed that the level of resting ventilation in COPD represented 20-30% of the ventilatory reserve, compared to only 5% in normal individuals. A substantial effort is therefore required to breathe, resulting in a tendency towards dyspnoea. Cropp (1984) in a study published in abstract form related breathlessness in COPD and normals to fractional respiratory drive (ie  $P_{0.1}$  over maximal inspiratory pressure) and to fractional minute ventilation (ie  $\dot{V}_E$  over maximal voluntary ventilation). There was no significant difference in breathlessness (measured on a Borg scale) between the patients and the control group for any given fraction of ventilatory capacity or maximal inspiratory pressure.

#### 2) Hyperinflation

Hyperinflation per se has not been shown to be an important determinant of shortness of breath. However the consequences of hyperinflation may be important as the thoracic musculature must work at a mechanical disadvantage. Killian et al (1984) showed that breathing at an increased lung volume increased the breathlessness experienced during elastic loaded

breathing at least when  $f$  and  $V_t$  were simultaneously constrained. Sharp (1968) has shown in a study of 17 patients with COPD, that postural relief of dyspnoea was only evident in those who were the most hyperinflated. This suggests that adopting a more favourable position by sitting forward stretches the diaphragm and places it at a more favourable position on its length tension relationship, thus reducing the 'effort' needed for contraction. This reduction in effort or neural activation was confirmed by a reduction in diaphragmatic EMG activity. The work of Leblanc (1986) relating dyspnoea to the pressure required to inspire a breath as a fraction of  $P_{i\max}$  is in agreement with this as the pressure generating ability of the diaphragm will be impaired at higher lung volumes. McFadden (1973) found that the dyspnoea of acute asthma correlated with hyperinflation and sternocleidomastoid recruitment. During treatment and recovery from bronchoconstriction dyspnoea subsided as accessory muscle activity ceased but while hyperinflation persisted, indicating that muscle activity rather than hyperinflation was the important determinant of breathlessness.

Breathholding experiments in normal volunteers show that breathhold time is unchanged when the breath is held above FRC compared to breathholding at FRC, but that the onset of diaphragmatic contractions is delayed (Whitelaw 1987). The relevance of this finding in normal volunteers to the persistent hyperinflation of COPD is uncertain.

### Respiratory muscle fatigue

The increased ventilatory requirements and the mechanical disadvantage of the inspiratory muscles caused by hyperinflation places them at risk of fatigue. However the role of respiratory muscle fatigue in the causation of breathlessness is unclear. Roussos (1982) found EMG evidence of fatigue

during exercise in COPD, whereas other authors (Kongragunta 1988) have been unable to show any evidence of fatigue during exercise limited by extreme dyspnoea despite showing EMG evidence of fatigue when the same subjects breathed through a resistor.

Several studies have examined the effect of respiratory muscle rest on dyspnoea and functional performance. Cropp (1987) and Guitierrez (1988) showed that assisted ventilation improved respiratory muscle performance and exercise tolerance as well as relieving dyspnoea. The authors postulated that the mechanism was relief of inspiratory muscle fatigue. Direct evidence of respiratory muscle fatigue as a cause of breathlessness in stable COPD is presently lacking.

#### Intrinsic Positive End Expiratory Pressure (PEEPi)

The persistently prolonged expiratory time in severe COPD causes expiration to be interrupted by the onset of the next inspiration. This means that the inspiratory muscles must overcome both the lung elastic recoil pressure and the positive intrathoracic pressure acting as a threshold load before inspiratory airflow can begin. This added load increases the effort required to breathe and has been investigated recently. The application of CPAP helps overcome the threshold load and reduces the work of breathing. Petrof (1990) in a study of 7 patients during weaning from mechanical ventilation showed that dyspnoea and work of breathing per litre of ventilation was reduced by the application of CPAP at the expense of modest (435 +/- 96 mls) increases in end expiratory lung volume. O'Donnel et al (1988) and Petrof and co workers (1990) have examined the effect of CPAP on exercise in COPD. The former study found that CPAP reduced dyspnoea in patients with COPD but had no effect in normal controls. Petrof (1990) showed that CPAP reduced inspiratory muscle effort and improved dyspnoea in 5 out of 8 patients and that the amelioration of dyspnoea was related to

reduction in the pressure time integral of oesophageal pressure but not to the pressure time integral of trans-diaphragmatic pressure. In this study there was no change in end expiratory lung volume with the addition of CPAP.

### Airflow obstruction

In COPD the dominant respiratory impedance is resistive, in addition the degree of airflow obstruction is greater during expiration due to expiratory airway collapse. Airflow obstruction has been studied both in normal individuals and in patients with airflow obstruction both by added external resistive loads and by pharmacologically induced bronchoconstriction. Both these interventions increase the sense of dyspnoea in both normal subjects and in COPD. Kelsen (1979) has shown in normal volunteers that the sense of effort was greater with bronchospasm than with an equivalent resistance produced by resistive loading. Schwarzstein (1991) has shown in study published recently in abstract form, that the sensation associated with bronchospasm is qualitatively different than with the application of an external resistor. These studies suggest that factors other than the increased work of breathing contribute to the type and intensity of breathlessness, and may suggest a role for airway receptors in modulating the dyspnoea of broncho-constriction. No data is available on similar experiments in COPD. Expiratory flow limitation by dynamic airway compression may also play a role in the dyspnoea of COPD. O'Donnell (1987) showed that increasing the degree of airway dynamic compression by means of an expiratory unloading device in a group of patients with COPD produced an unpleasant respiratory sensation in the absence of changes in end expiratory lung volume, possibly suggesting that airway mechanoreceptors modify the sensation of breathing. Further evidence of a role for airway receptors is provided in a study by

Taguchi (1989) published in abstract form which showed that dyspnoea due to bronchoconstriction could be reduced following airway anaesthesia whilst it had no effect on sensation with resistive loaded breathing. Another study by Millman et al (1982) showed that in normal subjects the occlusion pressure response to histamine induced bronchoconstriction could be abolished by airway anaesthesia.

In summary the sensation of dyspnoea in COPD is related closely to the effort of breathing, as suggested by the Length Tension Inappropriateness Theory of Campbell and Howell. However the sensation of effort may be modulated by other factors such as fatigue, airway calibre, airway compression, and changes in blood gas tensions.



### Measurement of dyspnoea

In general there are two methods for assessing the intensity of dyspnoea.

- 1) Assessment of dyspnoea by determination of the exertional task required to produce disabling breathlessness. This technique is routinely used in clinical assessment eg the MRC scale of breathlessness
- 2) Psychophysical methods of assessment of sensation which quantify the sensation of dyspnoea using scaling techniques.

### Clinical assessment of dyspnoea

Several scales of dyspnoea have been devised, all of which assign numerical values to the exertional task which produces a given level of dyspnoea. In 1959 Fletcher proposed a 5 point scale to assess dyspnoea and later the MRC scale (1960) was proposed which has subsequently been modified and used in many clinical trials, both epidemiological, diagnostic and therapeutic. McGavin (1978) described an oxygen cost diagram which is a combination of a visual analog scale upon which descriptor tasks are placed proportionate to their oxygen cost. Using the oxygen cost diagram the workers found a relationship between position on the oxygen cost diagram and 12 minute walking distance ( $r=0.6$ ) suggesting that the value of clinical assessment of dyspnoea could be improved if this scale was used routinely. More recently Mahler et al (1985) attempted to develop a clinical rating scale for dyspnoea which employed standard questions designed to induce consistency between observers. They assessed disability in three categories; functional impairment, magnitude of task needed to evoke dyspnoea and magnitude of effort needed to evoke dyspnoea. Using these concepts they devised a baseline dyspnoea index measuring 'background' breathlessness and a transitional dyspnoea index which represented the change in dyspnoea following therapeutic intervention. With this

complicated system they found significant correlations between 12 minute walking distance and base line dyspnoea,  $R=0.6$  and change in 12 minute distance and change in transitional dyspnoea score,  $R=0.33$ . However the system is complicated to use and seems unlikely to gain any wide clinical acceptance. Because of its complexity it is less useful in physiological studies than the psychophysical methods described below.

### Psychophysical methods of assessment of dyspnoea

Psychophysical tests have become widely accepted and their use has offered insights into the mechanism of breathlessness and perception of other respiratory stimuli. Psychophysics is the quantitative study of the relationship between a sensory stimulus and the evoked sensory response.

Psychophysical assessment can be divided into four domains:

- 1) detection - is there something there?
- 2) discrimination - is this different from that?
- 3) recognition - what is it?
- 4) scaling - how big is it?

Detection and discrimination are closely related and studies of load detection and discrimination during the early 1960's eventually gave rise to the length tension inappropriateness theory of breathlessness of Campbell and Howell.

More recently psychophysical techniques have been used in the scaling of added loads to the respiratory system. Using this technique reproducible levels of sensation are obtained for a given load and the Psychophysical Law of Stevens (1971) has been applied to respiratory sensation.

$$\Psi = K\Phi^B$$

$\Psi$  = sensation intensity,  $\Phi$  = stimulus intensity,  $K$  a constant and  $B$  an exponent.

Values for the power exponent  $b$  have been calculated in loaded breathing experiments and the rate of increase of sensation has been found to be significantly lower in patients with COPD (Gottfried 1978) suggesting that sensory adaption occurs in response to prolonged loading.

Similar scaling techniques can be applied to the assessment of breathlessness.

Scales may be either closed, ie the subject may place a sensation between two fixed end points, or open, in which any number chosen by the subject may be used to quantify his sensation. Open magnitude scaling has mainly been applied to loaded breathing experiments and although the method may be applied to exercise induced breathlessness comparison across individuals is not possible, and comparison within the same individual across time is questionable. Also the abstract nature of the scale makes it difficult for some individuals to grasp the concept. For these reasons interval and category scales are more useful in studying changes in breathlessness in groups of patients following therapeutic intervention.

#### The choice of scale for quantifying breathlessness

There are 2 commonly used scales for the quantification of breathlessness:

##### The visual analog scale

In this technique a straight line 100 to 200 mm in length serves as a continuum. Attached to it are verbal descriptors placed at either end of the line usually representing the extremes of the sensation under test, eg not at all breathless and maximally breathless. Stark and Gambles (1981) and others have shown that the VAS could be employed to assess breathlessness in normal healthy individuals and the relationship between breathlessness score and ventilation showed satisfactory within subject reproducibility. Subsequent studies by the same authors (Stark 1982) have applied the technique to the assessment of breathlessness in sub maximal

exercise testing in obstructive lung disease. They again found good within subject reproducibility of breathlessness scores and also a reproducible relationship between breathlessness and ventilation. In this study the anchor point for severe breathlessness was chosen by the patient as the breathlessness induced by specific task. Other authors (Wilson 1989) have found acceptable reproducibility of the visual analog scale using simple descriptors such as 'not at all breathless' and 'maximum'

### The Borg category scale

The Borg Category Scale (Borg 1970) was originally conceived for rating perceived exertion during an exercise test and has been successfully adapted to the study of respiratory sensation. The original Borg scale consists of 15 grades with numbers from 6 to 20. To every odd number was attached a verbal descriptor ranging from very light to very hard. This scale has been modified in an attempt to provide it with ratio properties (Borg 1982). The revised scale is from 0 to 10 a doubling in the numerical value represents a two fold increase in sensation intensity. The addition of the descriptors introduces categories but the patient is free to chose any number or fraction.

The variability of perceived breathlessness on exercise in COPD measured by the unmodified Borg scale has been studied by Silverman (1988). He examined the reproducibility of breathlessness in 6 patients with COPD during and after 3 incremental cycle exercise tests, two on the same day and one between 1 and 10 days later. Breathlessness score correlated with  $\dot{V}O_2$  and  $\dot{V}E$ ,  $R=0.92$ . The co-efficient of variation of the Borg Scores at 2 minute exercise and at end exercise were  $3 \pm 1\%$  and  $3 \pm 2\%$ . The variability was similar both within and between days. The variability of breathlessness assessed by modified Borg scales has been assessed by Wilson

(1989). Breathlessness scores were less on the second study day by 16% and less variable than the VAS which had a mean difference between tests of 27%. The test were performed between 2 and 6 weeks apart.

Recently VAS and Borg scales have been compared in both normal individuals (Wilson 1989) and in patients with COPD (Muza 1990). Both studies rated dyspnoea simultaneously during repeated cycle exercise testing. Muza found both measures of breathlessness correlated linearly with minute ventilation in all trials and when the values were converted to common units they correlated very closely as would be expected ( $R=0.99$ ). The between method variability is difficult to test. The co-efficient of variation of the scores for maximal breathlessness was 6 +/- 1% with VAS and 3 +/- 1% for Borg scale. In this study the Borg scale was unmodified and the VAS had no descriptors at either end. Wilson's study compared a VAS with descriptors and the modified Borg scale and found the Borg scale correlated more closely with ventilation than VAS, both studies showed the Borg scale was more repeatable than VAS.

These studies suggest that the Borg category scale is more robust than the VAS, and relates more closely to ventilation. Therefore this scale has been used in the measurement of breathlessness throughout this thesis

The modified Borg category scale

|            |                                           |
|------------|-------------------------------------------|
| <b>0</b>   | <b>nothing at all</b>                     |
| <b>0.5</b> | <b>very very slight (just noticeable)</b> |
| <b>1</b>   | <b>very slight</b>                        |
| <b>2</b>   | <b>slight</b>                             |
| <b>3</b>   | <b>moderate</b>                           |
| <b>4</b>   | <b>somewhat severe</b>                    |
| <b>5</b>   | <b>severe</b>                             |
| <b>6</b>   |                                           |
| <b>7</b>   | <b>very severe</b>                        |
| <b>8</b>   |                                           |
| <b>9</b>   | <b>very very severe (almost maximal)</b>  |
| <b>10</b>  | <b>maximal</b>                            |

### The respiratory system during exercise in COPD

Exercise in COPD is limited by respiratory mechanics (Jones 1971, Leaver 1971, Potter 1971, Stubbing 1980), unlike in normal individuals (Olafsson 1969) in whom the limiting factor is cardiovascular. Minh (1979) showed that the heart rates achieved during maximal exercise in COPD were low suggesting that cardiovascular factors are not a limiting factor. In COPD patients expiratory flows impinge on the maximum flow volume envelope early in exercise (Leaver, Potter, Stubbing) but in normal individuals the exercise flow volume loop does not reach the maximum flow volume envelope even on maximal exercise. During exercise in COPD the maximum effective transpulmonary pressure is not exceeded (Leaver and Pride 1971). To do so would exacerbate dynamic airway compression, and thus reduce expiratory flows. Similarly, during exercise, ventilation soon approaches 100% of MVV in COPD.

Some patients with severe COPD breathe along their maximal flow volume envelope even at rest. Thus the only way that expiratory flows can be increased is by a dynamic increase in FRC on exercise. This has been shown experimentally by Dodd (1984), Grimby (1970) and Stubbing et al (1980). Stubbing et al made direct measurements of FRC during exercise using an air conditioned body plethysmograph. They found that FRC increased to 113% of its resting value at maximal exercise, but that TLC remained unchanged. In contrast FRC in normal individuals fell during exercise. The increase in FRC on exercise while increasing expiratory flows places the respiratory muscles on a disadvantageous part of their length tension relationships, and increases inspiratory elastic work. These factors increase the work and reduce efficiency of the respiratory muscles, predisposing them to fatigue. The other strategy to increase ventilation during exercise available to patients with severe airflow obstruction is to prolong expiration and to

shorten inspiratory time ( $T_i$ ). Shortening  $T_i$  requires an increased velocity of contraction of the respiratory muscles which increases work.

Chest wall mechanics are altered during exercise in COPD. Sharp described paradoxical or incoordinate thoracoabdominal motion during MVV in COPD, and postulated that this leads to inefficiency of the ventilatory pump. Grimby et al (1973) have shown an increased abdominal contribution to ventilation on cycle exercise in COPD

### The assessment of exercise performance in COPD

Exercise performance may be assessed in several ways: by the formal exercise test in the physiology laboratory using cycle ergometry or progressive incremental treadmill testing or by methods which use a form of exercise more familiar to the patient such as step tests or timed corridor walking tests. The former methods have the advantage that ventilation and oxygen uptake together with oxygen saturation may be measured. However they are unfamiliar forms of exercise to the patient, especially in those with severe COPD and if performed to measure  $\dot{V}O_2$  max are exhausting for the patient and therefore unsuitable for repeated testing when assessing an acute therapeutic response.

A more suitable test in severely disabled patients is a sub maximal one which produces data about the respiratory response to a pre-determined work load. However this test has the disadvantage that it is an unfamiliar form of exercise to the patient and that instrumentation is usually required. It cannot give information about the overall degree of respiratory disability or the functional impairment which therapeutic intervention aims to relieve.

To measure this two forms of exercise test have been designed, the step test and the corridor walking test. The step test was first described by



Hugh Jones in 1952. It has the advantage that ventilation may be measured as the patient is essentially stationary, but the disadvantage that steady state  $\dot{V}O_2$  or  $\dot{V}E$  are not reached even after 10 minutes in patients with COPD. In addition the differences between repeated attempts are much greater than with corridor walks (Swinburn 1985).

### Walking tests

The 12 minute exercise test was developed as a test of fitness in young servicemen when it was recognised that the distance covered running in 12 minutes correlated highly with  $\dot{V}O_2$  max (Cooper 1968). In tests of endurance in fit young men steady state was not reached until 8 minutes of exercise. For these reasons 12 minutes was chosen as the test duration in submaximal exercise testing (Katch 1973).

The technique was first applied to patients with COPD by McGavin et al (1976) who described the 12 minute corridor walking test. The patient is instructed to cover as much ground as possible in 12 minutes, stopping as necessary but continuing as soon as able. The distance walked showed a learning effect. The maximum improvement in walking distance occurs between walks 1 and 2 but significant improvements also occur between walks 2 and 3. McGavin et al (1976) showed significant relationships between walking distance and the  $\dot{V}E$  and  $\dot{V}O_2$  achieved during cycle ergometry ( $r = 0.53$  and  $0.52$  respectively). The same group showed a correlation between walking distance and the limiting physical activity perceived by the patient using an oxygen cost diagram ( $r = 0.6$ ). However there was no relationship between 12 minute walking distance and the patients own estimate of 12 minute walking distance prior to the test.

Mungall (1979) assessed the variability of lung function tests and walking tests in a group of 13 patients with COPD on 6 occasions at 2-3 weekly intervals. Improvement in 12 minute walking distance occurred between

visits 1 and 2 and 2 and 3, but thereafter there was no significant increase in walking distance. Mean co-efficient of variation of 12 minute distance overall was 8.2% but if results from the first two days were excluded then the co-efficient of variation was 4.2%. Mungall found no correlation between distance walked and FEV<sub>1</sub>, FVC or TLC measured either by helium dilution or body plethysmography. Only transfer factor correlated with distance ( $r=0.67$ ). Most subsequent studies of walking tests have showed a similar lack of correlation between walking distance and lung function tests.

The main disadvantage of the walking test is that its self paced nature makes it liable to influence by motivation. Guyatt (1984) and Morgan (1983) have examined the effect of attitudes and beliefs and encouragement on walking distance in COPD. Guyatt showed that 6 minute distance was improved by 30 metres with encouragement, while Morgan et al found that mood and attitudes and beliefs were a better indicator of exercise capacity than FEV<sub>1</sub> and FVC.

Recently in an attempt to overcome the difficulties associated with the self paced nature of the corridor walking test Scott et al (1990) have described in abstract form the shuttle walking test which involves walking between 2 shuttles at increasing speed. If the initial promise of this test is borne out then it may be useful in assessing therapeutic response.

#### What is the optimum length of exercise test?

Butland (1982) compared 3 different lengths of walking tests; 12 minutes, 6 minutes and 2 minutes in patients with a range of respiratory diagnoses. He found that after an initial burst of speed patients walked at a constant rate. The variance of the longer test was greater which probably reflected greater discriminating power. The correlation between the tests was very high suggesting that patients select the speed which they are able to

maintain by experience, however the learning effect over the first 2 tests shows that walking tests are not a perfect mimic of the exercise of daily activities. Butland concludes that 6 minutes is probably the optimum length of walking test, representing a compromise between ease of performance for the investigator and patient, and discriminating power. Morice et al (1984) utilised the relatively constant speed during the majority of a walking test described by Butland et al to devise the 100 metre walking test. The time taken to cover 100 metres during the third minute of a walk is measured, the first 2 minutes walking is not used because of the initial burst of speed at the beginning of the walk. This test has found little acceptance and seems to offer no advantage over conventional walking tests.

Data from Swinburn et al (1984) suggests that a steady state VE and V02 were achieved after 6 minutes of walking of the 12 minute walking test. Thus 6 minutes is probably the optimum duration of a corridor walking test.

#### The cause of exercise limitation in COPD

Exercise may be limited by a variety of factors such as breathlessness, fatigue and pain in both normal subjects and in those with COPD. It is generally accepted that patients with COPD have limited exercise tolerance as a result of impaired respiratory mechanics. However in a study of 119 patients with COPD by Jones et al (1989) published in abstract form, cycle ergometry exercise was limited by leg discomfort in 31%, by dyspnoea in 26% and by both factors in the remainder.

Stubbing (1980) has shown that patients with severe COPD frequently breath along their maximum expiratory flow relationship at rest. In these individuals the increased ventilatory requirement of exercise may theoretically only be met by increasing the end expiratory lung volume above its resting level, thus allowing increases in expiratory flows,

alternatively shortening inspiratory time will allow a larger portion of the respiratory cycle for expiration which is usually the limiting factor. This increase in expiratory lung volume has been shown to occur in severe COPD experimentally by Stubbing and co-authors. As described previously the dynamic hyperinflation which occurs with exercise in COPD serves to increase expiratory flows but has the opposite effect on inspiratory flows since the inspiratory muscles must work at a greater mechanical disadvantage. Increases in end expiratory lung volume on exercise cause reductions in the maximal inspiratory pressures, work by LeBlanc (1986) suggests that dyspnoea is related to the ratio of the inspiratory pressure generated with a normal tidal breath to the maximum inspiratory pressure thus dyspnoea may be worsened.

Respiratory muscle fatigue offers an explanation of the ventilatory limitation to exercise in COPD. Studies in normal individuals (Supinski 1987) and in patients with COPD whilst exercising breathing through external resistances have shown that respiratory muscle fatigue does occur, and that it is associated with increased breathlessness or effort sensation compared to the non-fatigued state. However studies in patients with COPD exercising maximally have shown conflicting results. Bye (1985) and Roussos (1982) have shown changes in diaphragmatic EMG tracings consistent with muscle fatigue in patients with COPD on exercise. Other workers (Levine 1986 and Krongratunga 1988) have been unable to confirm these changes in patients with COPD when exercise was limited by intolerable dyspnoea despite showing EMG evidence of fatigue during resistive loading in these patients.

## THE EFFECT OF THERAPEUTIC INTERVENTION ON BREATHLESSNESS AND EXERCISE TOLERANCE IN COPD

Many studies have examined the effects of different interventions on exercise tolerance in COPD. These interventions may be grouped together broadly as pharmacological methods of modifying airway mechanics and physical methods directed towards improving the efficiency of the respiratory muscles by rehabilitation programmes and assisted ventilation in various forms. There have been fewer studies examining the effect of therapeutic intervention on the perception of breathlessness.

### Pharmacological Modulation of Breathlessness and Exercise Tolerance

While large numbers of studies have examined the effects of different groups of bronchodilators on exercise tolerance in COPD, fewer studies have studied the effects of bronchodilators on the perception of breathlessness and its relation to exercise tolerance. Mahler (1985), Chrystyn (1988) and Kongragunta (1988) have all examined the effect of theophylline on exercise tolerance in COPD with differing results. Kongragunta found no improvement in cycle exercise duration in a study examining the effect of theophylline on dyspnoea and diaphragmatic fatigue. In this study exercise was continued until limited by severe dyspnoea. There were no differences in exercise duration at equivalent levels of dyspnoea at exercise termination.

Mahler found that theophylline treatment reduced overall dyspnoea significantly, but had no effect on 12 minute walking distance. In contrast Chrystyn et al showed a linear dose dependant improvement in both 6 MD and breathlessness following treatment with theophylline.

Improvements in spirometry in all these studies were small. Chrystyn et al noticed a linear dose dependant fall in trapped gas volume, which they

proposed as a sensitive test of small airway function, proposing that the mechanism by which theophylline improved breathlessness and 6 minute walking distance was by bronchodilatation of small calibre airways.

The role of steroid treatment in COPD remains controversial, and studies of the effect of steroids on exercise performance and breathlessness also show conflicting results. Mitchell (1984) found that 12 minute distance improved following prednisolone treatment whereas O'Reilly (1982) found no improvement in 12 minute distance and Strain (1985) found no improvement in cycle ergometry duration. None of these three studies showed any reductions in the perceived breathlessness though this was not assessed in a quantitative manner.

Beta agonists are widely used in the treatment of COPD, often in high doses via a nebuliser. Leitch (1978) McGavin (1976) and Papris (1986) showed improvement in walking distance following beta agonist administration. There was no correlation between improvement in the spirometry and improvement in exercise tolerance. Connellan (1982) examined the effect of high dose (10 mg) Salbutamol in a group of irreversible patients with COPD. They noticed a dramatic improvement in walking distance with concurrent falls in RL and dynamic compliance. Unfortunately this study was not blinded in any way and no practice 12 minute walks were performed. Corris (1983) and Vathenen (1988) both examined the dose response effect of increasing doses of Salbutamol with contrasting results. Corris showed a significant dose related improvement in 12 minute distance whereas Vathenen et al were unable to show any additional benefit from Salbutamol compared to placebo despite the dose related improvements in spirometry with Salbutamol. However in this study the results were complicated by an excessive placebo improvement in walking distance.

The effect of anticholinergic therapy on exercise performance and breathlessness in COPD has been studied previously with conflicting results. Leitch (1978) in a comparative study of Salbutamol and Ipratropium Bromide showed a significant improvement in exercise performance with Salbutamol, but the improvement with Ipratropium Bromide failed to reach statistical significance. There were comparable changes in FEV<sub>1</sub> following administration of either drug. Brown et al (1986) showed that Atropine improved VE max but not maximum work load during cycle ergometry. They found that oxygen requirements were lower at a given work load following bronchodilator, presumably because of the reduced work of breathing consequent upon improvements in lung mechanics after bronchodilator. Recently Hay et al (1992) have shown that Oxitropium Bromide improves exercise tolerance and breathlessness in a group of patients with COPD. These improvements were independent of changes in FEV<sub>1</sub> or FVC.

Oxygen administration has been shown to improve six minute distance and dyspnoea (Leggett 1977) and increase maximal work rate during cycle ergometer exercise (Vyas 1971, Leggett 1977). The improvement in exercise tolerance was accompanied by an decreased minute ventilation, there were no changes in lung function following oxygen administration.

Breathing low density gases was reported in early studies to improve dyspnoea (Barach 1936, Grape 1960). More recent studies (Swidwa 1985) have failed to show any improvement in exercise tolerance breathing low density gases.

#### Rehabilitation and assisted ventilation

Patients with COPD are unable to generate large ventilatory pressures due to respiratory muscle weakness and develop respiratory muscle fatigue rapidly. For these reasons exercise programs have been designed to increase

maximal ventilation and thus improve exercise tolerance, reduce breathlessness and enhance the quality of life in patients with COPD. Training methods used include isocapnic hyperventilation, resistive and threshold inspiratory loading. Pardy et al (1981) have shown that all 3 methods are successful at increasing respiratory muscle strength and MVV. The improvement in exercise tolerance was not consistent. Keens (1977) and Belman (1980) found improvements in exercise capacity after training in a group with cystic fibrosis, whereas Levine (1986) was unable to show any benefit from training in a group with COPD.

#### The effect of mood and attitude on breathlessness and exercise ability

The disability caused by any disease is multifactorial, this is especially true in chronic disease which interfere with the ability to perform everyday tasks. The degree of impairment is thus in part determined by psychological factors rather than the physical consequences of the illness. Morgan (1983) has shown that walking distance is as much related to mood, attitude and beliefs as it is to FEV1 or FVC, while Guyatt (1984) showed that exercise performance could be significantly improved by encouragement. Breathlessness (a multifactorial sensation) is likely to be influenced by psychological factors. Studies on the effect of mood are not extensive. However Burns and Howell (1969) found that disproportionately severe breathlessness was more likely in individuals who suffered depressive illness, anxiety or obsessional states traits than in more stoic individuals. Similarly threshold load detection is greater in anxious dependent patients (Hudgel 1982). Twin studies have demonstrated environmental in ventilatory load detection experiments (Kawakami 1984) Quality of life questionnaires have been designed to identify the impact of COPD on patients lives and determine factors related to performance (Guyatt



1987). Guyatt (1987) demonstrated that the quality of life was only weakly related to the degree of airflow obstruction.

Thus factors such as mood are likely to influence the measurement of breathlessness and exercise performance and changes in mood or attitude may confound longer term studies of therapeutic intervention. The influence of changes in these factors in acute studies such as the ones detailed in this thesis seems less likely therefore and therefore have not been examined

## CHOLINERGIC CONTROL OF THE AIRWAYS

Cholinergic fibres travel in the vagus and synapse in parasympathetic ganglia which are located in the airway wall. From these ganglia short postganglionic fibres travel to airway smooth muscle and mucous glands. In animals electrical stimulation of the vagus causes bronchoconstriction and mucous secretion through acetyl choline release. Prior administration of a muscarinic receptor antagonist such as atropine blocks this bronchoconstriction.

Cholinergic innervation is greatest in the large airways and diminishes peripherally. Animal studies suggest that cholinergic effects are greatest in the large airways and is minimal in small airways. Human studies have suggested that cholinergic bronchoconstriction predominantly involves the large airways. Normal humans have resting bronchomotor tone since atropine causes bronchodilatation and edrophonium (an acetyl cholinesterase inhibitor) bronchoconstriction (Barnes 1987).

Cholinergic effects are mediated by muscarinic receptors on target cells in the airways. Smooth muscle muscarinic receptor activation results in rapid phosphodiesterase hydrolysis and formation of inositol triphosphate which releases intracellular calcium. Receptor activation also inhibits adenylate cyclase and reduces cyclic AMP in airway smooth muscle.

### Cholinergic mechanisms in airway disease

In COPD there is structural narrowing of the airways which is irreversible. In addition there is a degree of vagal bronchomotor tone. Whilst in normal airways this tone has little effect on airway calibre, when the airways are narrowed the same degree of tone will have a much more pronounced effect on airways resistance (which is proportional to the fourth power of the radius). Reversing this tone will have significant bronchodilator effect. Anticholinergic drugs cause bronchodilatation in normals, asthmatics and in

patients with COPD. The effect of the drugs is variable between patients perhaps owing to different degrees of bronchomotor tone. Anticholinergic drugs are competitive antagonists of acetyl choline, so the bronchodilator effect is related to the dose given until maximum blockade of acetyl choline is achieved. Five muscarinic receptor antagonists have been identified, all have been described in the airways, but the relevance of all of these groups of receptors to airway disease and therapy is not certain. Both available anticholinergic bronchodilators ipratropium bromide and oxitropium bromide are non selective muscarinic receptor blockers.(Barnes 1987)

## OXITROPIUM BROMIDE

Oxitropium bromide is a non selective muscarinic antagonist. It is a quaternary ammonium compound (which may account for its unpleasant taste) which is derived from scopolamine.

### Dose response

Early published dose response studies by Peel and Anderson (1984(1)) in 12 patients with COPD concluded that the optimum dose of oxitropium was 400-600 micrograms. Frith (1986(1)) et al in a study of 24 patients with moderate to severe airways obstruction compared the effect of oxitropium in 3 doses (100,200 and 300 microgram) with placebo and with fenoterol. They found that doses of 200 and 300 mcg produced an equivalent increase in FEV1 (though the improvement was only statistically greater than the 100 mcg dose 4-8 hours after administration of the drug. The improvement in FEV1 at all doses was less than that following 400mcg inhaled fenoterol, though the effect of the 2 drugs was additive. The effect of oxitropium was more prolonged than that of the B agonist. The authors conclude that the optimal dose of oxitropium bromide is 200mcg. Other studies performed by the manufacturers Boehringer Ingelheim also suggest that the optimal dose is in the region of 200 micrograms daily (Calverley 1992).

### Time course of action

Peel and Anderson (1984(1)) in their study in COPD found that the maximum increase in FEV1 following 600 mcg oxitropium was 2-3 hours post administration. Similarly Frith et al (1986(2)) found the peak effect of the drug to be 2 hours post administration though an effect within 5% of peak was reached after only 10 minutes. Peel et al (1984(2)) in a study of 24 asthmatics compared the time course of action of 200mcg oxitropium bromide and 80mcg ipratropium bromide and found no difference in the improvement in FEV1 up to 10 hours post drug. Studies comparing the actions

of B agonists and oxitropium in both COPD (Frith 1986(1)) and asthma (Tukiainen 1985) found that the peak action of the B agonists (fenoterol and salbutamol) was earlier, between 0.5 and 1 hour compared to 2 hours following oxitropium however the duration of action of the anticholinergic was more prolonged with the peak being sustained for up to 180 minutes following oxitropium and for up to 60 minutes following fenoterol. The effective clinical duration of action of oxitropium is difficult to measure, and may depend on the magnitude of the peak bronchodilator response. However in the study of Frith et al the time taken for the FEV1 to decay to 50% of its peak value was 5.5 hours. Other unpublished work sponsored by the manufacturers suggest that the time to 50% of peak action may be up to 11 hours. All of these studies have relied on objective lung function measurements, either FEV1 (Peel (1984(1) and Frith or PEFr (Peel 1984(2)). One study by Flohr (1979) measured airways resistance, but no assessment of the duration of action of any bronchodilator has been made using measures of subjective improvement.

The reason for the use of the anticholinergic bronchodilator oxitropium bromide in the majority of experimental work contained in this thesis is its relatively 'pure' bronchodilator action with low systemic absorption and lack of cardiovascular side effects which might influence exercise performance.

In Summary:

- 1) Mechanical factors secondary to structural damage in large and small airways limit exercise in COPD.
- 2) Mechanical and possibly chemical factors eg hypoxia influence dyspnoea at rest and during exercise.
- 3) Lung volumes are increased in COPD and this is associated with high levels of intrinsic PEEP which may be an additional and conventionally undetectable modifier of dyspnoea.
- 4) Exercise capacity may be influenced by small degrees of bronchodilatation, but prediction of response is difficult.

These factors lead to a number of interrelated questions which can be addressed within a limited number of clinical studies and which form the basis of the work reported in this thesis.

## THE INDICATIONS FOR THE WORK CONTAINED IN THIS THESIS

As stated previously, most therapy in COPD is symptomatic and aims to reduce dyspnoea and improve exercise capacity. The relative roles of the different factors contributing to dyspnoea is uncertain as is the appropriateness of particular clinical, physiological and radiographic markers of disease severity. This thesis describes a series of studies in which these problems are addressed.

1) Helium dilution and plethysmographic lung volume measurement techniques both have problems in the presence of significant airway obstruction. I have assessed the reliability of X ray derived lung volumes as an alternative method of lung volume measurement in normal individuals and in patients with COPD.

2) Bronchodilators reduce breathlessness and improve exercise tolerance in COPD even in the absence of large spirometric changes. Little data is available on the relationship between the altered lung mechanics (in particular changes in lung volume and airways resistance) brought about by bronchodilatation, and the improvements in perceived breathlessness and exercise tolerance. I have examined the effect of both anticholinergic and beta agonist bronchodilators on exercise tolerance and breathlessness in relation to changes in spirometric measures. In addition I have examined the effect of the anticholinergic bronchodilator oxitropium bromide on lung volume and airways resistance and related these changes to changes in exercise tolerance and perceived breathlessness.

3) Trapped gas volume has been proposed as a sensitive indicator of response to bronchodilators in patients with obstructive pulmonary disease, and as a

predictor of functional improvement. No data is available on the reproducibility of this measurement.

4) Pharmacologically induced bronchoconstriction increases breathlessness. Little data is available on the relationship between the increased sensation of breathlessness and the altered lung mechanics brought about by histamine induced bronchoconstriction, nor of the effect of oxitropium bromide on bronchial reactivity in relation to altered lung mechanics. I have performed histamine challenges on patients with COPD and have measured changes in breathlessness induced by bronchoconstriction. I have related these to changes in mechanical measures of lung function. In addition I have examined the effect of prior bronchodilatation on this relationship and coincidentally examined the effect of bronchodilatation on bronchial reactivity in COPD.

5) Bronchodilators may alter ventilation perfusion relationships within the lung with consequent alterations in blood gas tensions. Alterations in oxygen saturation may have an independent influence on the perception of breathlessness. I have measured changes in oxygen saturation both at rest and during corridor exercise before and after bronchodilator administration and related changes to changes in exercise tolerance and breathlessness.

6) PEEPi imposes a threshold load on the respiratory muscles but little is known of the relationship between changes in PEEPi and breathlessness in response to bronchodilator administration. Alterations in the mechanical impedance to breathing by bronchodilatation may alter the ventilatory and perceptual responses to hypercapnia and hypoxia. No data is available on the effect of bronchodilators on these responses in COPD. I have examined



the effect of oxitropium bromide on breathing pattern, respiratory mechanics and perception of breathlessness during reflex stimulated breathing.

In summary:

Studies relating changes in breathlessness and exercise performance to changes in spirometry after bronchodilator have demonstrated only weak relationships. Changes in other commonly measured variables may be more appropriate markers of functional improvements. This has been examined. Helium dilution and plethysmographic lung volume measurements are subject to artefactual errors however radiological methods of lung volume determination are free of these artefacts. Thus the thesis has examined the validity of radiological measurements in COPD.

The sensation of breathlessness is closely related to respiratory muscle function which is in turn related to changes in lung volume and the load under which they operate. Mechanisms of breathlessness have been examined in a series of experiments examining the effect of bronchodilation and bronchoconstriction on lung mechanics and breathlessness



## MEASUREMENT OF LUNG VOLUMES BY X-RAY PLANIMETRY

### Introduction

The measurement of lung volumes from X-rays offers a potentially useful method of estimating lung volumes in COPD and other conditions if it can be shown to be reproducible, and compare reproducibly with other methods. The main theoretical advantage of X-Ray derived lung volumes is that they are free from the artefactual errors caused by prolonged time constants for gas mixing and pressure equilibration which confound the helium dilution and body plethysmographic techniques respectively.

Hyperinflation is a common description of the chest radiograph in reports of X-rays in patients with COPD. The radiographic features of hyperinflation include low flat diaphragms, an increased AP diameter of the chest, an increased retrosternal space, anterior bowing of the sternum, kyphosis, a small vertical heart and visible costophrenic attachments (Felson 1973). None of these features allows any quantitative measure of lung volume to be made. In a study examining the hyperinflation of acute asthma only lung height measured on AP chest X ray changed significantly between acute attack and convalescent films and then only by 0.43cm (Blackie 1990). For this reason several techniques have been developed for quantitative estimation of lung volumes from chest radiographs.

Radiographic methods were first used to estimate lung volumes by Hurtado and Fray in 1933. They measured the area of the lungs on the PA chest radiograph and multiplied this by the PA diameter of the chest measured externally. Kovach et al (1956) treated the chest radiograph as a paraboloid of revolution of the PA radiograph whilst Bernhard et al (1960) assumed that each lung and the heart comprise a series of elliptical cylinders and the diaphragm 1/8 of ellipsoid. Pratt (1967) described a

method of estimating lung volume by using radiograph lung area and a regression equation. Pierce et al (1979) described a method which utilised the developing power of computers. The co-ordinates of the boundaries of the chest wall, heart, diaphragm and spine from PA and lateral chest radiographs were entered into a computer using a digitising board and from this shape information the volume of the chest and contained structures derived.

In the method of Pierce et al the pleural margins are traced. In the PA radiograph the pleural margin follows the inner rib margins, the heart boundary includes the arch of the aorta, and the spine outline follows the tips of the lateral pedicles of the vertebrae to take account of the associated muscle masses (figure 1.1). In the lateral view the pleural boundary follows the inner border of the sternum anteriorly and the inner rib margins posteriorly. Where rotation of the chest displaces the rib margins then a line between the 2 margins is taken. Similarly a line midway between the 2 hemi diaphragms is followed. The heart outline again includes the arch of the aorta as far posteriorly as the anterior margin of the spinal mass. This is drawn 1cm in front of the vertebral bodies to allow for the oesophagus and descending aorta. Posteriorly the boundary of the spine follows that of the chest (figure 1.2). The planes of the PA and lateral chest x-rays were aligned using the arch of the aorta as a common reference point. The resulting planes are then divided into 200 slices. The cross sectional shape of each slice is assumed to be between that of the rectangle generated by the dimensions of the planes of that slice, and that of an ellipse. This cross sectional area was found to be the closest to that of cross sectional areas determined from serial CT sections of the chest. From these measurements the volume of the chest is calculated. From the total chest volume, the volumes of the heart, great vessels,

sub-diaphragmatic thoracic volume and spinal volume (including paravertebral musculature) are subtracted to give the total lung volume. From the total lung volume a correction factor is calculated to take account of the volume of the blood within the lungs and the solid tissue of the lungs leaving, after all these calculations, the volume of air within the thorax.

With the advent of cheap and powerful computing a commercial package using the principles of the method of Pierce et al is now available manufactured by P K Morgan Ltd, Chatham, Kent. I have used this method to determine lung volumes from radiographs taken at total lung capacity and functional residual capacity in normal volunteers and in subjects with severe COPD and have defined the relationship between X-ray derived lung volumes and those by helium dilution and plethysmographic methods in these groups of patients. I have also evaluated the accuracy of this X ray planimetric method in determining changes in lung volumes measured concurrently by other methods.

### Subjects

10 normal volunteers were recruited from the staff of the hospital. All were male because of the small risks associated with radiation in women of child bearing age. No normal volunteer had a history of lung disease (table 1.1)

12 patients (9 male) all with a history of COPD irreversible to oral steroids were recruited from the out patient clinics at Fazakerely Hospital. All were current or ex-smokers. All complained of breathlessness on exertion (table 1.2).

All subjects, both normal and COPD patients gave written informed consent. The study was approved by the hospital ethical committee.

## Methods

PA and lateral chest x-rays were taken with the subject seated (to be comparable with the other methods of determination of lung volume). Ventilation was monitored during the course of the exposure of the chest x-rays by the subject breathing from a water spirometer (PK Morgan Ltd) modified by the addition of a CO<sub>2</sub> absorber to which was added oxygen to maintain a constant volume of gas within the spirometer.

One PA chest x-ray was taken at a total lung capacity (figure 1.3) and then immediately afterwards a further chest x-ray was taken at FRC. The subject was instructed to stop breathing at FRC by the physician supervising, who determined the moment to stop breathing by observation of the movement of the water spirometer. The position of the lateral chest x-ray was then taken up (figure 1.4) and a further pair of x-rays were taken at TLC and FRC, ventilation being again monitored with the water spirometer.

The X ray tube to film distance was constant at 6ft throughout the study. Lung volumes were then determined by body plethysmography with the subject panting at 1Hz while supporting the cheeks and by helium dilution. The value used for analysis from the body plethysmography was the mean of three measurements and for helium dilution the mean of two measurements. Details of both methods are given elsewhere in this thesis.

Lung volumes were determined using the planimeter in the normal volunteers by DS and in the patients with COPD by DS and a trained non medical research assistant YJ

Figure 1.1  
The outline traced on the PA radiograph

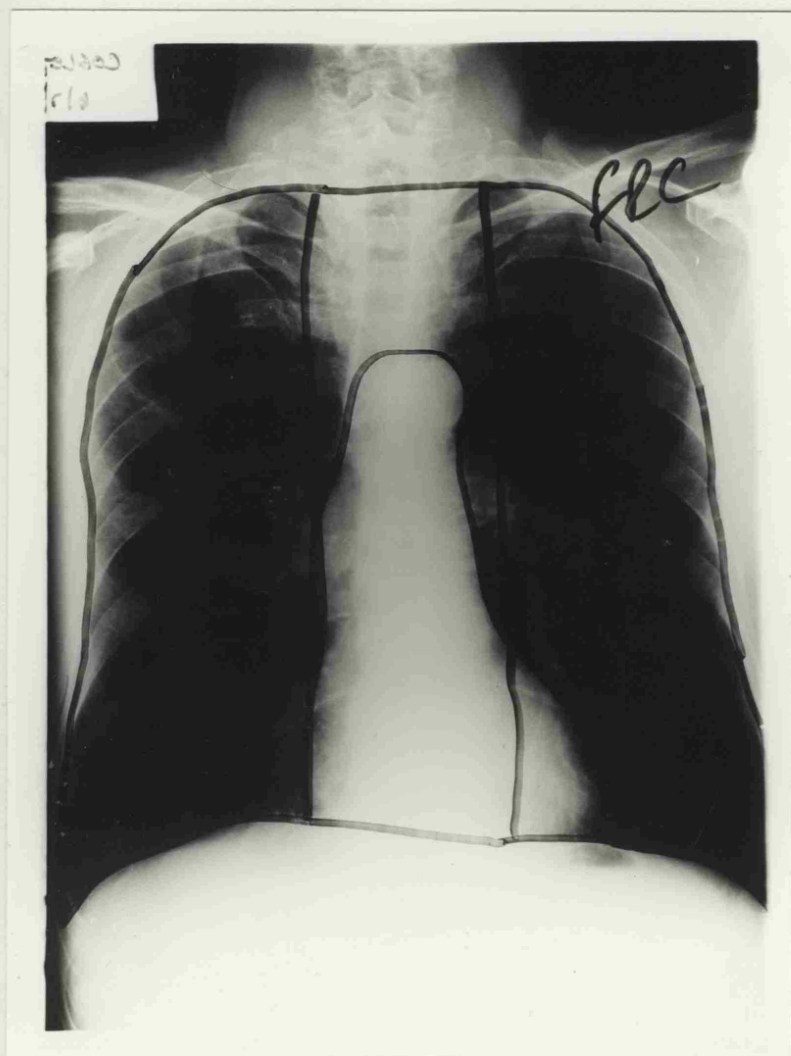


Figure 1.2  
The outline traced on the lateral radiograph

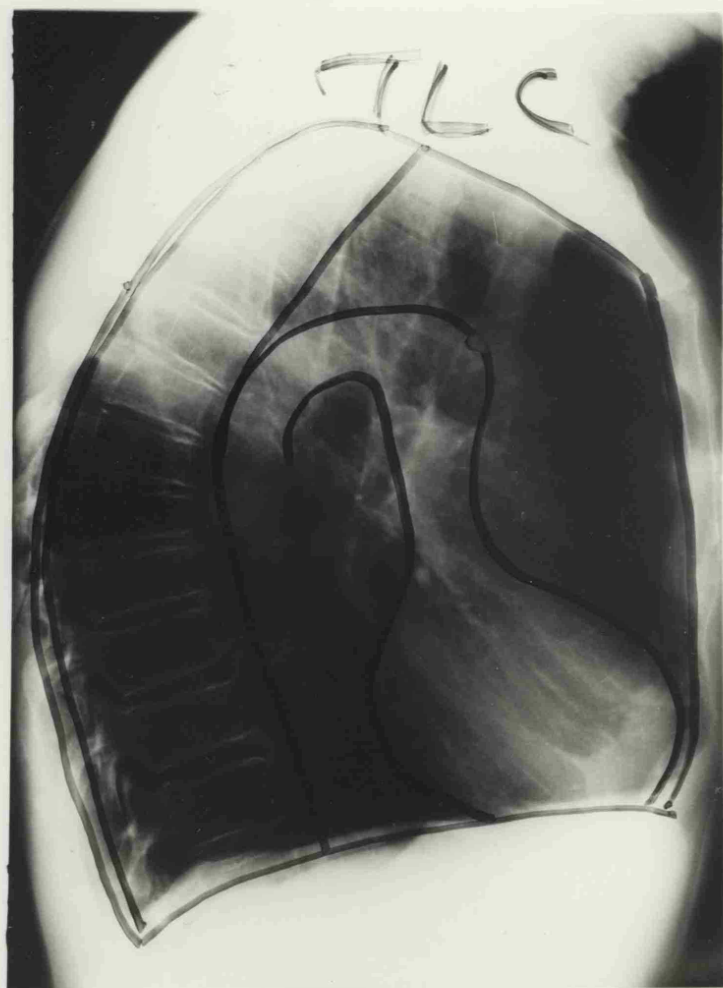


Figure 1.3  
The position adopted for the PA radiograph





Figure 1.4

The position adopted for the lateral radiograph



## Results

Normal volunteers: Mean(SD) values of TLC for the group were similar, X ray 7.13(1.02)L and 7.08(1.12)L for the body plethysmograph. However the differences between the 2 techniques was large within individual patients, as expressed graphically in figure 1.5.

Values for FRC for the group were significantly ( $p < 0.001$ ) lower when measured by plethysmography compared to planimetry, and again agreement between the 2 techniques within individual patients was poor (figure 1.6) Inspiratory capacity measured by X ray planimetry (the difference between TLC and FRC measured from X rays) and that measured on the spirometer during exposure of the X rays was good when mean data is analyzed 2.51(1.04) by planimetry and 2.8(0.4) by spirometer; however agreement within patients was poor (figure 1.7)

Table 1.1)

The biographical details of the patients and normal volunteers in the X ray lung volumes experiment

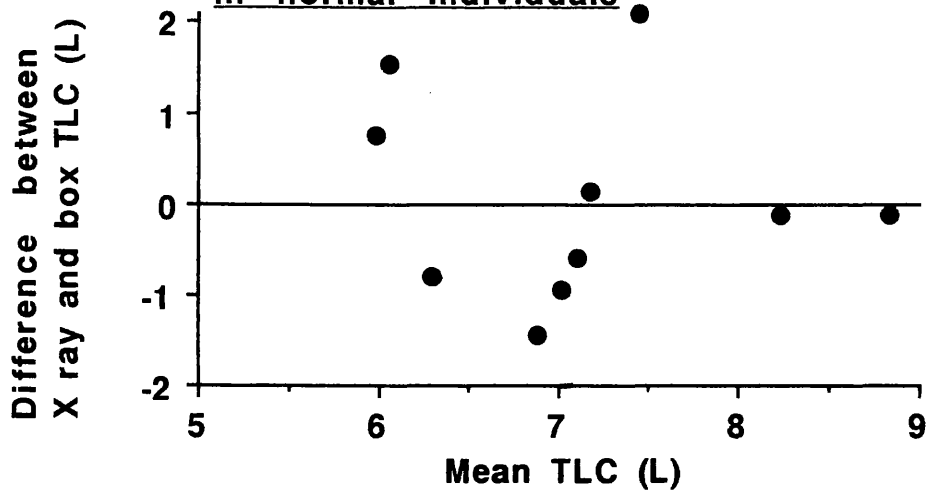
| mean(SE )     | Normal volunteers<br>(n = 10) | COPD patients<br>(n = 12) |
|---------------|-------------------------------|---------------------------|
| Age (years)   | 32.7(2.7)                     | 61.8(3.3)                 |
| FEV1 (L)      | 4.87(0.4)                     | 0.84(0.07)                |
| FEV1 (% pred) | 102(3)                        | 28(8)                     |
| FRC (L)       | 3.6(0.85)                     | 6.33(0.29)                |
| TLC (L)       | 7.08(1.12)                    | 7.68(1.24)                |

Table 1.2)

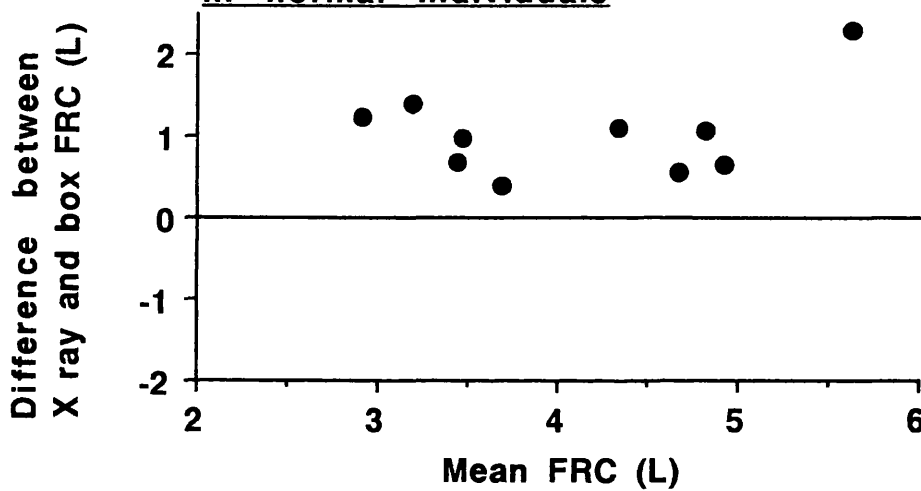
Comparison of lung volume measurements by X ray, box and helium dilution techniques(L)

| mean<br>(SD) | X ray DS   | X ray YJ   | Box        | Helium     |            | Insp cap   |
|--------------|------------|------------|------------|------------|------------|------------|
| FRC          | 6.17(1.63) | 6.27(1.59) | 6.33(0.99) | 4.95(0.86) | X ray      | 1.18(0.28) |
| TLC          | 7.24(1.46) | 7.23(1.46) | 7.68(1.24) | 6.60(1.10) | spirometer | 1.06(0.83) |

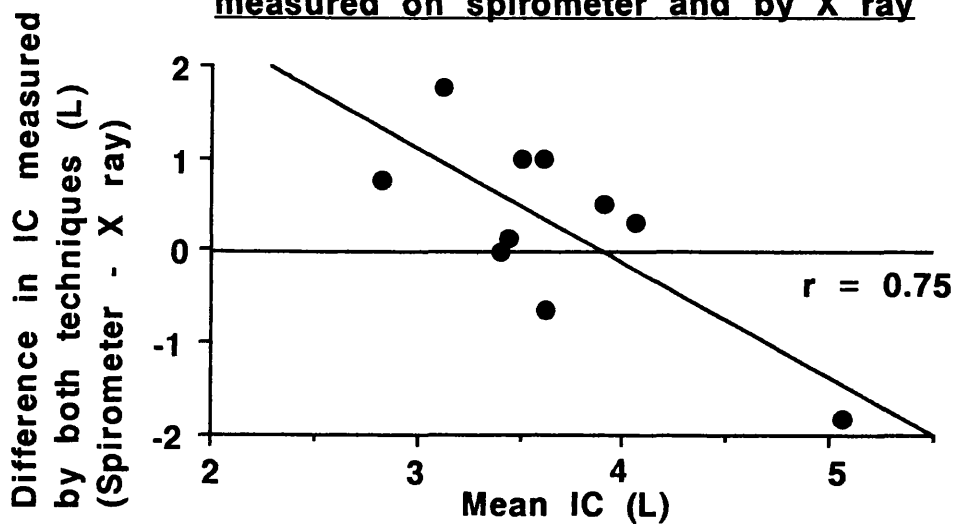
**Figure 1.5** Difference between box and X ray TLC in normal individuals



**Figure 1.6** Difference between box and X ray FRC in normal individuals



**Figure 1.7** Difference between inspiratory capacity measured on spirometer and by X ray



#### Patients with COPD:

There were no significant differences between the lung volumes measured by either body plethysmography or planimetry. Agreement between observers for planimetric lung volume measurements was good (figure 1.8). Those obtained by helium dilution were significantly lower than by the other 2 methods. The 95% confidence intervals of the differences between box and X ray were wide, mean difference between box and X ray TLC -0.44L (95% CI -2.4 to 1.52L) (figure 1.9) and between box and X ray FRC -0.16L (95% CI -2.42 to 2.12L) (figure 1.10). Mean inspiratory capacities measured by X ray and spirometer were not significantly different, though again the 95% confidence intervals were wide (95% CI -1.46 to 1.73L) (figure 1.11). Interobserver difference between X ray lung volumes was small, mean TLC difference 0.01L (95% CI -0.67 to 0.69L) and between FRC measurements 0.12L (95% CI -0.39 to 0.57L). The results of the lung volume measurements by the 3 techniques are summarised in table 1.2. There was no relationship between the difference between box and X ray TLCs and lung volume. FRC measurements tended to be larger by X ray compared to box at low lung volumes and vice versa for larger lung volumes. There was no correlation between the difference between lung volumes measured planimetrically and by plethysmography and the degree of airflow obstruction.

**Figure 1.8**      Between observer difference  
in planimetric FRC

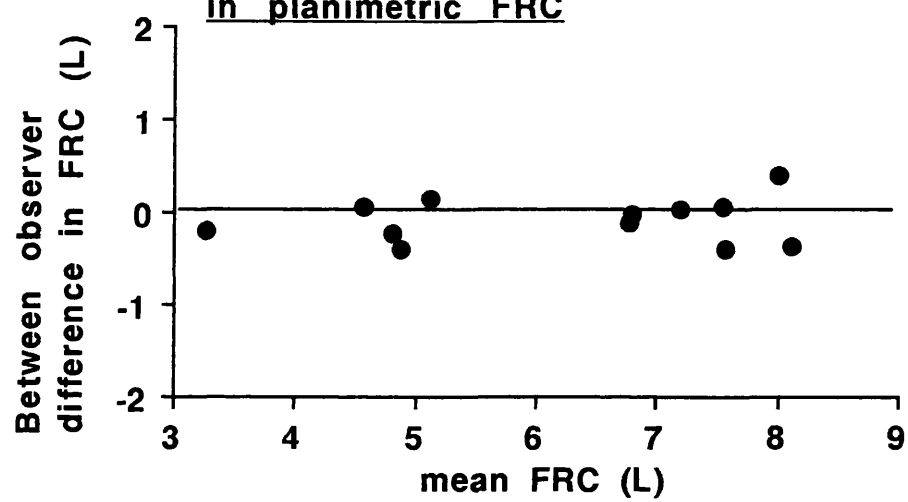


figure 1.9

Between technique difference in  
TLC in COPD patients

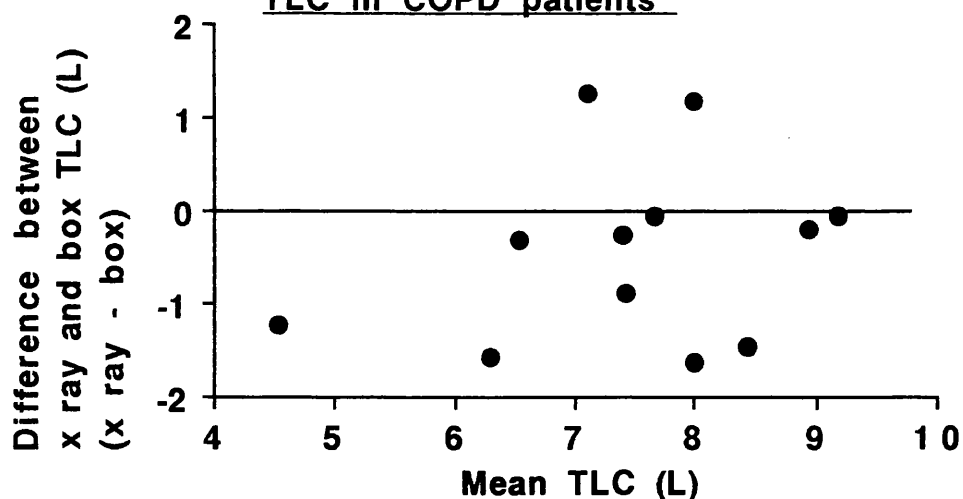


Figure 1.10

Between technique difference in FRC  
in COPD patients

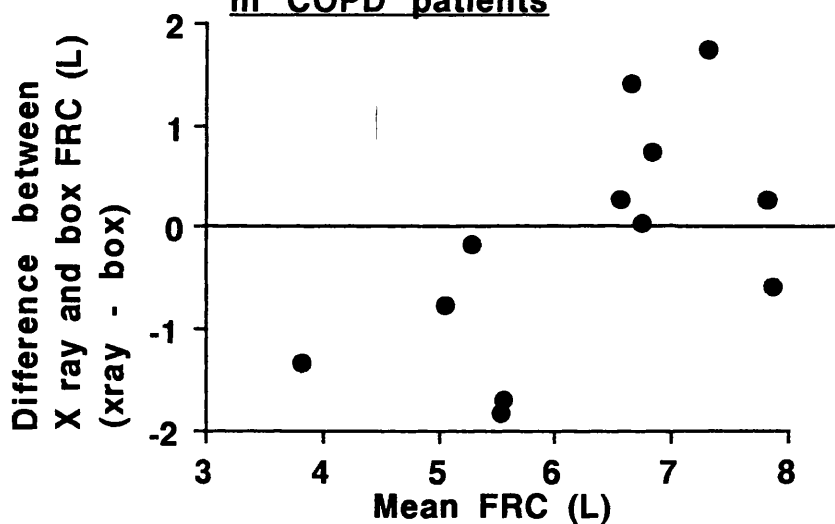
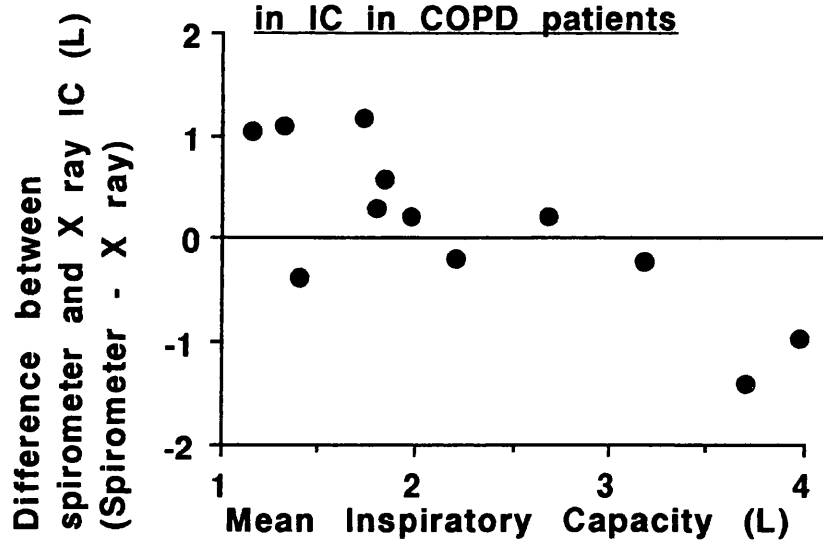


Figure 1.11

Between technique difference  
in IC in COPD patients



## Discussion

These data show that lung volume measurements using this X ray planimetric method do not relate closely to the more accepted methods of body plethysmography and helium dilution in either normal individuals or patients with COPD. Furthermore this planimeter does not accurately measure known changes in lung volume measured concurrently on a spirometer. These limitations make the planimeter unsuitable for individual patient studies, though mean group data may be useful in retrospective studies where X rays are available, but no other lung volume measurement has been made. However these data should be treated with caution. Recent studies (Kilburn 1990) have advocated the use of the planimetric method of Harris et al (1971) in the measurement of lung volumes in retrospective studies of asbestosis. In Harris' description of the method comparison with other methods was made, and a correlation (an inappropriate statistical test) of 0.86 between X ray lung volumes and plethysmographic lung volumes is given. For comparison the correlation between box and X ray in this study was 0.75. Kilburn has also suggested that X ray lung volumes may also be used to calibrate a body plethysmograph, which is clearly highly inappropriate. Other authors (Rothstein 1989) have used the method of Loyd et al (1966) to determine changes in TLC during acute asthma since it is not subject to time constant artefact in the presence of airflow obstruction unlike other lung volume measurement techniques, and have concluded that a fall of 0.29L in TLC occurs on recovery from severe bronchoconstriction.

The wide differences between lung volume measurements by different methods within individuals in this study is disappointing. However the differences observed are not dissimilar to previous studies using this and other planimetric techniques. Loyd reports a mean difference of 66ml(SD 739ml) in a series of 10 subjects and Pierce et al in their original description of



the method used in this study quote differences between X ray and box of 0.72(0.37)L in 35 normal volunteers which they attributed to lung tissue, water and blood volumes measured by the X ray technique but not by plethysmography. In this study lung volumes were slightly higher by the plethysmographic method rather than the X ray technique in the subjects with COPD. This could be attributed to overestimates of true lung volume by the plethysmographic technique because of the presence of significant airflow obstruction. This data agrees with work by Pare et al (1983) who, using another radiological technique, found that TLC was 0.5L less measured radiologically compared to the value from a constant pressure plethysmograph using mouth pressure to derive TGV. Interestingly the mean difference was only 0.27L when TGV was derived from oesophageal pressure. Possible reasons for the lack of a close relationship between box and X ray measurements are the difficulty in closely following the boundaries both of chest wall and intrathoracic structures on chest radiographs. This is particularly a problem when trying to define the boundary of the chest wall among the associated shoulder musculature at the apices and in tracing the great vessels in poorly penetrated lateral films. Likewise identifying both leaves of the diaphragm on lateral x rays is sometimes difficult. Further exposure to X rays to obtain satisfactory images from which to obtain lung volumes is difficult to justify either as a research or clinical tool when reliable alternative methods are readily available. Alternatively the differing positions adopted during the exposure of PA and lateral X-rays to ensure the best views of lung fields may result in changes in chest wall configuration between views. Attempting to construct a 3 dimensional image of the thorax from the coordinates of the boundary of the chest on PA and lateral chest X rays can only be at best an estimate if the shape from which the composite image is constructed changes between

views. In order to quantify the effect of altered posture on lung volume, measurements were made in the normal volunteers in the plethysmograph both with the arms raised to mimic the position of the lateral chest X ray and in the usual position supporting the cheeks. TLC was higher  $7.32(0.31)L$  with the arms raised compared to the usual position supporting the cheeks ( $7.1(0.32)L$ ) ( $p < 0.05$ ). While some of this difference may be due to a compliant upper airway causing over estimates of lung volume (vide infra) (though this effect should be minimal in the absence of airflow obstruction) some may be due to the altered posture. Pierce et al report reductions in vital capacity of  $0.71(0.16)$  and  $0.18(0.12)L$  respectively when assuming the positions for PA and lateral chest X rays when compared to the normal relaxed position, and applied a correction factor for this when calculating lung volumes. These changes in vital capacity do imply changes in chest wall configuration between the PA and lateral chest X rays, and clearly a lung volume derived from different shapes which change between measurements will have a greater variability than a volume derived from a single measurement.

In conclusion, the measurement of lung volumes by radiographic techniques whilst having theoretical advantages in the presence of airflow obstruction has too great a variability compared to other methods to be practically useful in physiological studies. It may still have a role in retrospective studies where only group changes are of interest.

## THE EFFECT OF OXITROPIUM BROMIDE ON WALKING DISTANCE AND BREATHLESSNESS IN COPD.

### Introduction

The aims when treating any condition are to cure or slow the progress of the disease, and to alleviate any unpleasant or disabling symptoms. For patients with COPD no curative therapy is available apart from lung transplantation which is available to only a very small minority of patients, usually relatively young patients with Alpha 1 antitrypsin deficiency. The rate of decline of lung function may be slowed towards normal by complete abstinence from cigarettes. Therapy is therefore directed towards improvements in breathlessness and/or improvements in exercise tolerance that will allow the patient a greater functional capacity during daily living. These may be assessed by the use of scaling techniques to estimate the magnitude of perceived breathlessness and by self paced walking tests to estimate overall functional ability

### Methods

35 patients with COPD (individual biographical data is given in the appendix to this thesis) were recruited from outpatient clinics of Fazakerley Hospital. All gave a history of breathlessness for at least 1 year, and had an FEV1 of less than 50% predicted (Knudson 1976). All were known to be irreversible (change in FEV1 of < 200ml and < 15%) following 2 weeks of 30mg oral prednisolone within the 4 years preceding the study. None had any significant concurrent illness, in particular none suffered from any cardiac or other respiratory disorder or any problem which limited mobility. Patients with glaucoma or prostatism were excluded because of the possible risk for anticholinergic side effects. All patients were stable at

the time of the study and none had received oral steroid during the 1 month period preceding entry into the study. All subjects were able to use a metered dose inhaler correctly (checked by DS) All patients gave written informed consent. The study was approved by the local ethical committee.

The modified Borg scale linearises sensation of breathlessness or perceived effort within an individual and is useful to compare changes in sensation across groups. Because it has fixed end points (though in theory a subject may choose a score of more than 10) the data of breathlessness scoring is not normally distributed. For this reason non-parametric statistical methods have been used. However because of the limited number of numerical values little information regarding the distribution of breathlessness is provided by quoting median and range therefore mean data of breathlessness scores is given in table 2.2.

### Protocol

Patients attended on 4 consecutive days where possible, and when this was not feasible (in 2 patients) then visits 1 and 2, and 3 and 4 were on successive days. All visits were at the same time of day (afternoon or evening). Patients abstained from oral bronchodilators (beta agonist and theophyllines) for at least 24 hours, anticholinergic bronchodilators for at least 12 hours, and beta agonist inhalers for at least 6 hours prior to each visit to the laboratory. Caffeine containing drinks were prohibited during attendance at the hospital. Patients received standard refreshment of a sandwich and a soft drink during the 1 hour rest period in the middle of each study day following administration of the trial drug.

On visits 1 and 2 flow volume loops were performed. Lung volumes and airways resistance were determined in a constant volume body plethysmograph

(PK Morgan Ltd). 6 minute walking distance was assessed prior to medication, and breathlessness was measured using a modified Borg category scale at rest and at the end of the 6 minute walk by asking the question 'How breathless do you feel now'. No encouragement was given during the walk, but it was stressed at the beginning of each walk that the aim was to cover as much distance as possible in 6 minutes stopping if necessary but beginning again as soon as possible. During the walk and for 1 minute after pulse and oxygen saturation were recorded each minute from a pulse oximeter (biox 3700e) carried by a technician who walked behind the patients. If the patient needed to stop during the walk then pulse and oxygen saturation were recorded then also.

Oxitropium bromide 200mcg or placebo were administered from a metered dose inhaler in double blind random fashion and after 1 hours rest, flow volume loops, lung volume and airways resistance measurements were repeated.

On days 3 and 4 all the above lung function tests were performed, and in addition lung volumes were determined by a helium dilution method (mean of 2 measurements) before and after medication. An additional 6 minute walk was performed after medication with similar measurements of breathlessness score and oxygen saturation.

All flow volume loop measurements were performed seated, using the same 12L rolling seal spirometer (PK Morgan Ltd) by the same person (DS). This spirometer was attached to a dedicated IBM compatible computer (Samsung 6000). The computer and rolling seal spirometer were calibrated daily, and the calibration verified by adding a known volume of air to the spirometer. Flows were calculated by electronic differentiation of the volume signal. The values for FEV1, FVC and PEFr quoted are the best value of each from any of 3 technically acceptable attempts. In addition to measuring these simple spirometric variables, the software used also calculated F25, F50,

F75 and FEF25-75 together with peak inspiratory flow. Tidal flow volume loops were superimposed upon the maximum flow volume loops at the correct absolute lung volume. From these tidal flow volume loops peak tidal flows were derived manually. The values of derivatives of the flow volume loop other than FEV1, FVC and PEFr were taken from the loop which had the largest sum of FEV1 and FVC.

All plethysmographic lung volume measurements were performed using the same PK Morgan constant volume body plethysmograph by the same person (DS). This computerised plethysmograph was run using software utilising new algorithms for the calculation of the slopes of  $P_{mouth}$   $B_{box}$  plots. These new algorithms allow the measurement of lung volume from each one of the panting manoeuvres during a test run. This is achieved using Fourier analysis to calculate the fundamental slope of each panting manoeuvre, thus eliminating both box pressure drift and environmental artefact. The mean of all the slopes is calculated to give a thoracic gas volume measurement.

Panting frequency during all measurements was controlled during all tests by instructing the patient to breathe in time with an electronic metronome set to 120 beats per minute. Subjects were taught to breathe in on 1 beat and out on the next. Patients were tutored until they were consistently able to produce 'closed'  $P_{mouth}$   $P_{box}$  loops.

The value used in analysis is the mean value from 3 measurement runs.

Helium dilution functional residual capacity was determined by the standard rebreathing technique (McMichael 1939). Rebreathing was continued until the helium level was stable (a change of less than 0.05% over 2 consecutive 30 second periods). The volume of the spirometer was maintained at a constant level by the addition of oxygen. CO<sub>2</sub> was absorbed by a canister filled with

soda lime fitted to the spirometer. After each determination of FRC, after equilibration had occurred, a slow vital capacity manoeuvre was performed to determine TLC and its subdivisions. Any further change in the helium concentration after this was disregarded to minimise the risk of artefactual errors caused by an inadequate seal on the mouthpiece and consequent gas leakage during the manoeuvre.

Measurements of lung volume were performed 1 hour after administration of the trial medication. All measurements were performed in duplicate, each measurement being separated from its fellow by at least 15 minutes. All measurements were performed in a relaxed sitting position on the same piece of equipment. The value used for analysis was the mean of the 2 measurements.

Airways resistance was measured in the plethysmograph. Patients were seated in the plethysmograph and were taught the technique of panting in time with a metronome at 1Hz both with the shutter open and closed. Patients chose their own panting lung volume for each test. Between 4 and 6 inspiratory and expiratory efforts were made with the shutter open and closed. The software used to calculate airways resistance used similar algorithms to those which calculated FRC. The mean of 3 measurements was used in analysis. In addition to mean airways resistance, inspiratory and expiratory resistances and specific airways conductance were also calculated.

## Results

32 of the patients who started the trial managed to complete all 4 days. The 3 who withdrew (patients 2,11, and 25) did so after the first day, 2 because they found the protocol too tiring, and 1 because she was unable to satisfactorily master the technique of panting against a closed shutter during plethysmographic measurements in order to produce reproducible plots of Pmouth against Pbox when measuring thoracic gas volume.

There were no significant differences in baseline walking distances on any of the four days of the study when analyzed by one way analysis of variance. In addition there was no evidence of any learning effect over the first three days.(fig 2.1) The variability of six minute walking distance is derived from the data from days three and four to exclude any possible learning effect from the two training days. This variability data is expressed graphically in figure 2.2.

Oxitropium produced a modest but highly significant improvement in walking distance compared to placebo, the mean improvement being 31.1 metres over that obtained on the placebo day when walking distance fell after medication( $p < 0.005$ ) (table 2.1)



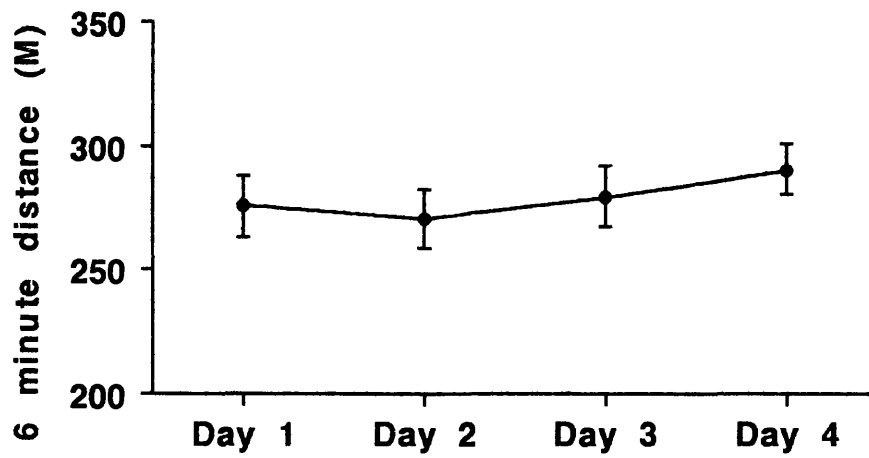
Table 2.1 The effect of oxitropium bromide on walking distance

| All mean (SE) | Oxitropium  | Placebo     |
|---------------|-------------|-------------|
| Pre drug      | 278.6(9.9)  | 291.4(12.5) |
| Post drug     | 298.4(10.8) | 280.1(14.0) |

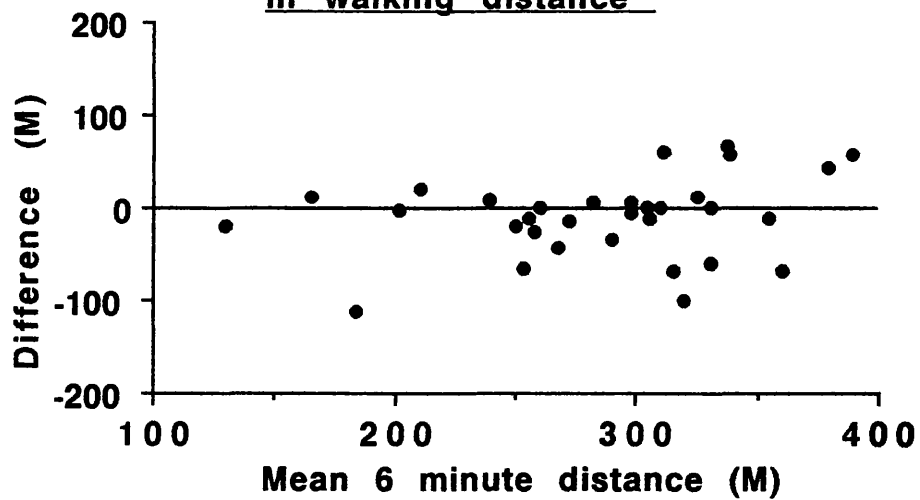
Table 2.2 The effect of oxitropium bromide on breathlessness

|             | Placebo   |           | Oxitropium |           |
|-------------|-----------|-----------|------------|-----------|
| mean(SD)    | Pre       | Post      | Pre        | Post      |
| Resting     | 2.03(1.2) | 2.43(1.5) | 2.16(1.6)  | 1.89(1.3) |
| End of walk | 3.82(2.4) | 4.14(2.3) | 3.48(1.9)  | 3.09(1.9) |

**figure 2.1**      **6 minute distance on all 4 days [mean(SE)]**



**figure 2.2**      **Between day difference**  
**in walking distance**



### Changes in breathlessness in response to oxitropium bromide

Both resting and final breathlessness fell significantly following oxitropium compared to placebo,  $p < 0.005$  for both assessments of breathlessness (table 2.2). The increase in breathlessness from start to finish of the walk was not significantly altered by oxitropium, though patients walked further for a similar increase in breathlessness. There was no correlation between improvements in either resting or end of walk breathlessness and the improvements in 6 minute distance.

### Discussion

These data show that administration of oxitropium bromide results in significant improvements in exercise tolerance and breathlessness, both at rest and at end exercise. The improvement in walking distance is in line with other studies in similar groups of patients using different classes of bronchodilators (Papris 1986, Berger 1988 (1), Chrystyn 1988 and Leitch 1978, but contrasts with the lack of improvement in walking distance following 40 mcg inhaled ipratropium bromide in the small comparative study by Leitch et al. The reason for the discrepancy of results may be the drug dosage and relative bronchodilator potency between the two studies. 200mcg oxitropium bromide produces bronchodilatation equivalent to 80mcg ipratropium bromide (Peel 1984). Hay et al (1990) examined the effect of oxitropium on exercise performance measured by cycle ergometry and 6 minute walks and reported significant improvements in exercise tolerance measured by both methods, the improvement in 6 minute distance being similar to this study.

The lack of the learning effect on the first 2 days is at variance with other published studies (McGavin 1976) and may be due to some of these

patients being familiar with 6 minute walking tests from previous studies. The lack of a placebo response also contrasts with previous studies (Vathenen 1988). The falls in walking distance and increases in breathlessness following placebo may be due to the relatively strenuous nature of the protocol in these severely obstructed patients. There was no relationship between reductions in either resting or end of walk breathlessness and improvements in walking distance in this group of patients. Although both resting and end of walk breathlessness were reduced by oxitropium the increase in breathlessness during the walk was not significantly different following bronchodilator. This is because patients may adopt differing strategies during a 6 minute walk when breathlessness is improved by a bronchodilator. They may walk further to achieve a similar level of breathlessness, or alternatively walking speed may be similar to the pre medication speed and the patient may accept less breathlessness at the end of the walk. Factors causing people to adopt one or other strategy may be the motivation of the patient to cover a larger distance, or the extent to which walking speed has been 'learnt' in order to avoid intolerable breathlessness. Short lived beneficial alterations in lung mechanics may only have limited effect on the walking speed which has been learnt and reinforced over many years in these severely obstructed patients. For these reasons subjective changes in breathlessness may be a more sensitive measure of improvements in lung mechanics following bronchodilator than improvements in exercise performance. The clinical application of 6 minute walking tests is limited by the possible learning effect, the effect of mood and motivation and also the wide 95% confidence intervals which we and others have demonstrated. Newer tests of exercise performance such as the shuttle walking test (Scott 1990) may not have some of these limitations.

The measurement of breathlessness is simply done, and provided there is no large placebo effect it may be a useful assessment in patients with severe COPD.

## SPIROMETRY AND SPIROMETRIC BRONCHODILATOR REVERSIBILITY AND THEIR RELATIONSHIP TO BREATHLESSNESS AND EXERCISE PERFORMANCE

### Introduction

I have demonstrated that oxitropium bromide improves both breathlessness and exercise tolerance in COPD. However the clinical application of the 6 minute walk is limited and so a relationship between improvements in breathlessness and commonly used physiological tests has been sought. Assessment of bronchodilator reversibility is useful diagnostically in management of asthma, and is increasingly being used to define those groups of patients with COPD who will benefit from a particular therapy in particular in the assessment of suitability for home nebuliser treatment (O' Driscoll 1990, Nisar 1990, Teale 1991). For these reasons bronchodilator reversibility testing is one of the most commonly requested lung function tests. The improvement sought and measured is an improvement in FEV 1 and/or FVC (or PEFr in domiciliary studies). These are easily obtained measurements which the physician understands, and which in asthma provide a guide to the effectiveness of therapy. However improvements in spirometry have little relevance to the patient with severe COPD whose interest lies in the relief of disabling dyspnoea and improvement in exercise tolerance. The belief amongst those requesting reversibility tests is that a large improvements in spirometry or PEFr equate with large functional and symptomatic improvements, and are therefore an indication to use a particular therapy in long term treatment. This is an assessment which few would question. Unfortunately the converse is also true and patients who have relatively small spirometric improvements, often within the variability of the measurement, following bronchodilator trials are frequently denied long term therapy. The lack of spirometric improvement

being used as a justification to withhold a drug in the belief that it will do no good.

Patients often report improvement in symptoms and exercise capacity following bronchodilators in the absence of large improvements in spirometry. Several studies (Mungall 1979, McGavin 1976) have shown that reductions in FEV1 and FVC correlate poorly with measures of functional impairment. Likewise improvements in spirometry after bronchodilator do not relate well to improvements in exercise tolerance (Connellan 1982, Berger 1988, Chrystyn 1988). If spirometrically defined bronchodilator reversibility is to be of use in COPD then the measurements of 'improvement' obtained in the laboratory must relate reproducibly to functional and symptomatic improvements. This chapter relates the observed improvements in exercise performance and breathlessness following oxitropium to changes in spirometry.

### Methods

The protocol and methods of determining spirometric variables are detailed above.

Relationships between spirometric variables and walking distance were determined by calculating Pearson correlation coefficients. Relationships between spirometric variables and breathlessness were by Spearman Rank Correlation. Baseline variability of spirometric measures was assessed by 1 way analysis of variance.

### Results

#### The variability of simple spirometric measurements.

The between day variability of the pre medication values of FEV1, FVC and PEFR on the 4 days of the study are shown graphically in fig 3.1

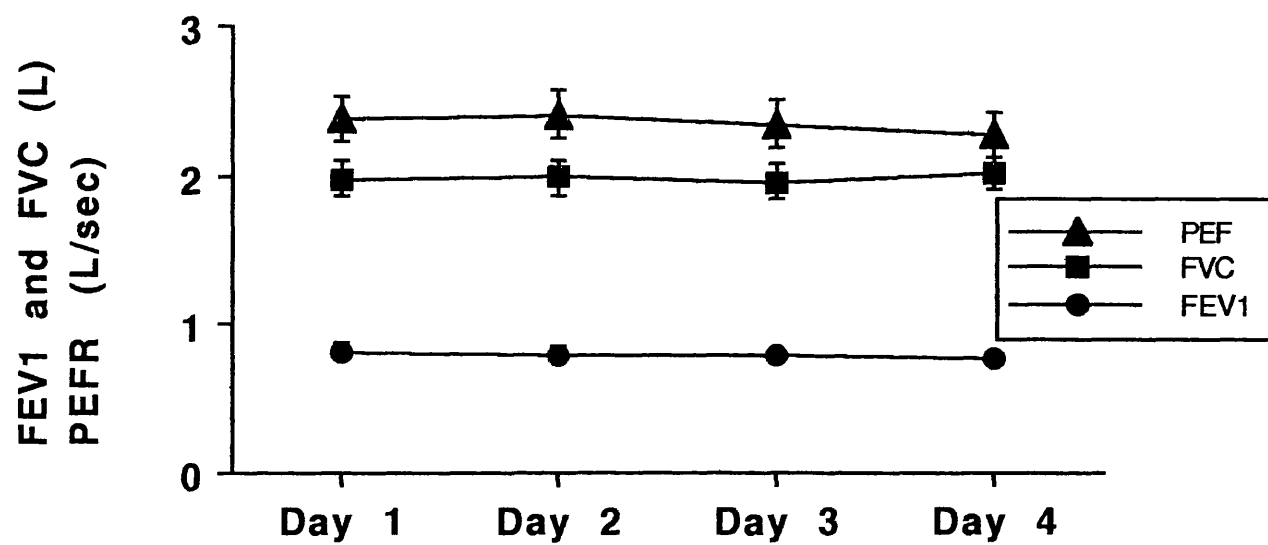
There were no significant differences between baseline spirometric variables on any of the 4 study days.

The 95% confidence intervals within and between days for FEV1, FVC and PEFR are summarised in table 3.1. Between day 95% CI are derived from days 3 and 4 pre medication, within day variation is pre and post placebo from the final 2 days of the study. There was no relationship between the variability of the measurement and the size of the measurement.

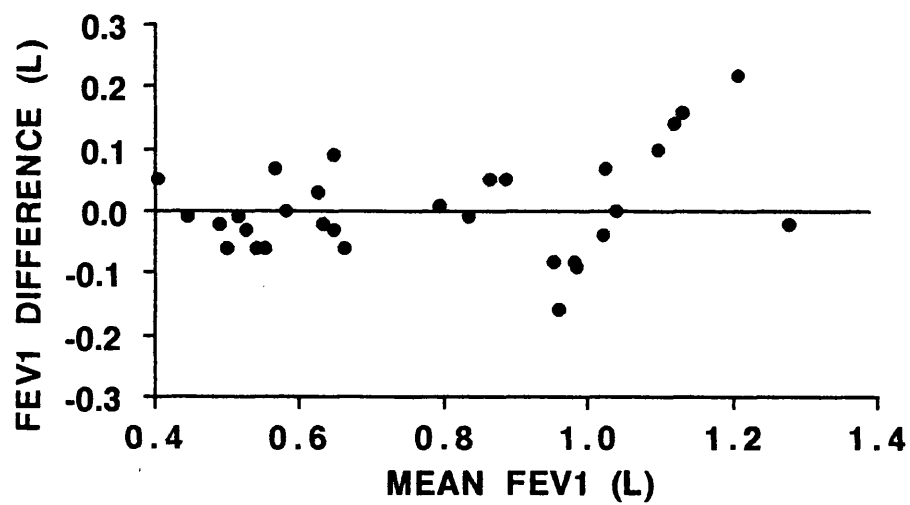
The between day variability of FEV1, FVC and PEFR are expressed graphically in figures 3.2 - 3.4



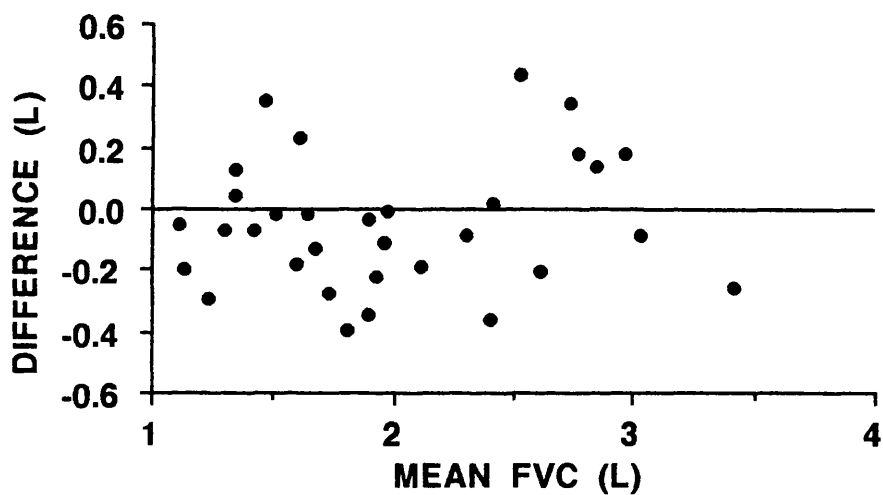
**Figure 3.1**      **Baseline spirometric values from all 4 days**



**Figure 3.2**      Between day difference in FEV1



**Figure 3.3**      Between day difference in FVC



**Figure 3.4**      Between day difference in PEFR

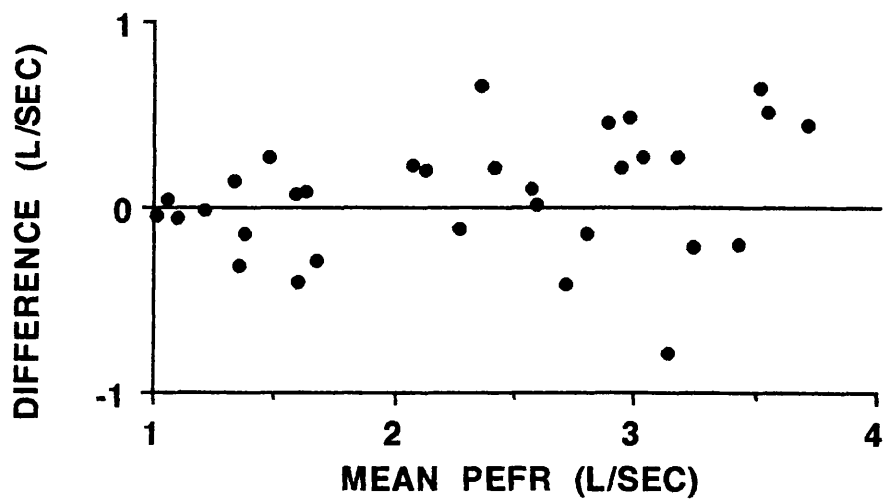


Table 3.1 The 95% confidence intervals within and between days for spirometric measurements

|              | Within day 95% CI | Between day 95% CI |
|--------------|-------------------|--------------------|
| FEV1 (L)     | +/- 0.174         | +/- 0.16           |
| FVC (L)      | +/- 0.34          | +/- 0.42           |
| PEFR (L/sec) | +/- 0.5           | +/- 0.66           |

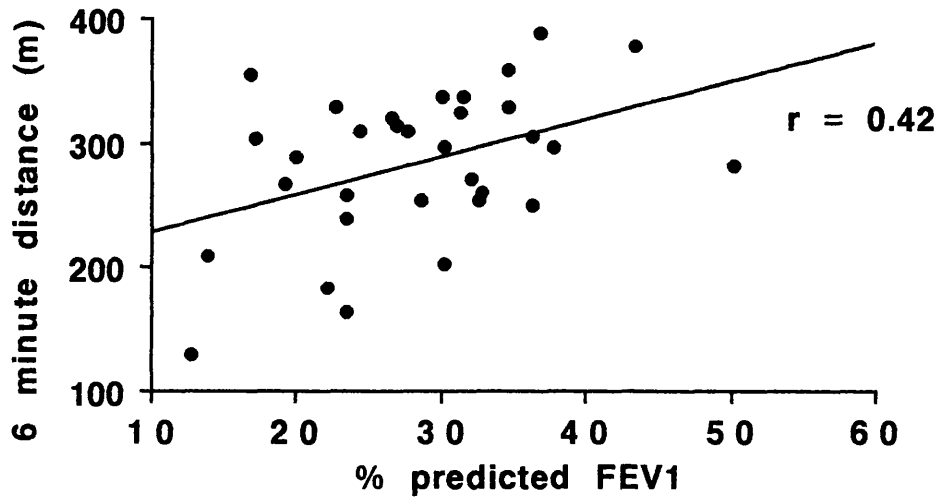
(The very small differences in mean values have been ignored)

### The relationship between spirometry, breathlessness and exercise performance

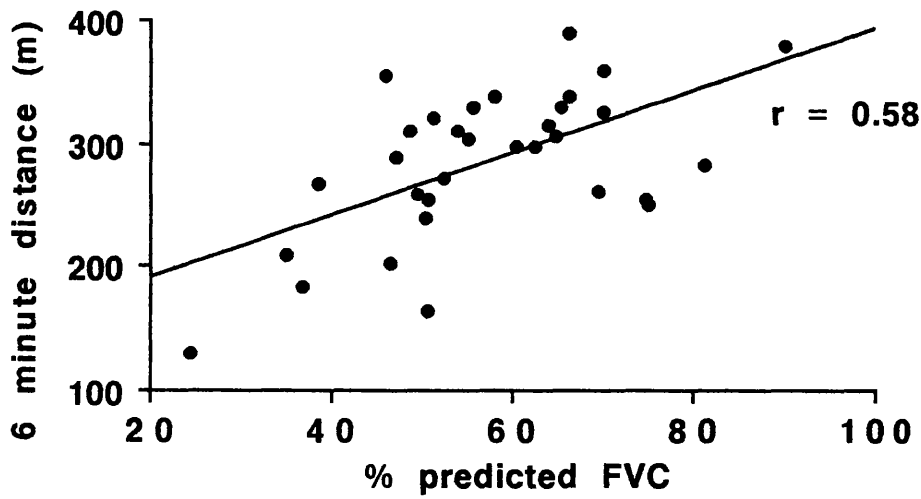
The relationships between spirometry and walking distance and breathlessness are from the mean pre treatment data from days 3 and 4 of the study to exclude any possible learning effects over the first 2 days. Pre treatment FEV1 and FVC correlated only weakly with 6 minute distance,  $r=0.34$  ( $p<0.05$ ) and  $r=0.4$  ( $p<0.05$ ) for FEV1 and FVC respectively. Percent predicted FEV1 and FVC were related more strongly with mean baseline walking distance  $r=0.42$  ( $p<0.02$ )(figure 3.5) and  $r=0.58$  ( $p<0.001$ )(figure 3.6) respectively. There was no relationship between PEFr or percent predicted PEFr and walking distance.

There were no significant relationships between any spirometric variable and the Borg scale assessment of breathlessness.

**Figure 3.5**    Percent predicted FEV1 and walking distance



**Figure 3.6**    Percent predicted FVC and walking distance



### Assessment of bronchodilator reversibility

Weir and Burge have suggested 4 possible ways of expressing bronchodilator reversibility:

1) As change in absolute value of FEV1 greater than the spontaneous variability of the measurement. The choice of the value used as the threshold is somewhat arbitrary. Tweeddale (1987) defined the short term variability of FEV1 and FVC in a large group of individuals with COPD, and found the 95% confidence intervals of the variability of the measurement to be unrelated to the size of the FEV1. In this study the 95% confidence interval for FEV1 was 160mls and for FVC 330mls, but in a previous study by the same authors in normal subjects and patients with obstructive airways disease the 95% confidence intervals for FEV1 were somewhat larger at 190ml (Tweeddale 1984).

2) As a change expressed as a percentage of the initial prebronchodilator FEV1 (% initial). When results are expressed in this manner small absolute changes become large percentage changes for patients with a low starting FEV1, so that those with the greatest spirometric impairment will show the greatest reversibility with any change in FEV1.

3) As a change expressed as a percentage of the predicted FEV1 (% predicted).

4) As a percentage of the 'possible' reversibility (Postma 1986) ie

$$\frac{\text{postbronchodilator FEV1} - \text{prebronchodilator FEV1}}{\text{predicted FEV1} - \text{prebronchodilator FEV1}} \times 100\%$$

Weir and Burge (1991) have also advocated using changes in FVC in addition to FEV1 in the assessment of bronchodilator reversibility. Measurements of reversibility should ideally be independent of the starting FEV1. Weir has shown that % 'possible' reversibility is related to the starting FEV1, and

Table 3.2 Reversibility to inhaled and nebulised salbutamol on the 2 occasions it was tested (n = 35)

| All mean (SE)                          | Test 1     | Test 2     |
|----------------------------------------|------------|------------|
| Pre test FEV1 (L)                      | 0.85(0.06) | 0.83(0.06) |
| Reversibility to 200mcg salbutamol (L) | 0.15(0.02) | 0.15(0.02) |
| Reversibility to 5mg salbutamol (L)    | 0.17(0.03) | 0.19(0.03) |
| Reversibility 200mcg salbutamol (%)    | 20(3.1)    | 19(2.7)    |
| Reversibility to 5mg salbutamol (%)    | 22(3.6)    | 23(3.6)    |

Table 3.3 Reversible and irreversible groups defined by increase in FEV1> 200ml following 5mg nebulised salbutamol (N = 32)

| [all mean<br>(SE)] | change in<br>fev1 (L) | FEV1 (L)       | FVC (L)        | PEFR<br>(L/sec) | FRC box<br>(L) | TLC box<br>(L) | FRC He<br>(L)  |
|--------------------|-----------------------|----------------|----------------|-----------------|----------------|----------------|----------------|
| Rev (n=17)         | 0.36<br>(0.03)        | 0.86<br>(0.06) | 2.26<br>(0.15) | 2.38<br>(0.22)  | 6.03<br>(0.39) | 7.21<br>(0.56) | 5.02<br>(0.31) |
| Irrev (n=15)       | 0.1<br>(0.01)         | 0.68<br>(0.05) | 1.68<br>(0.12) | 2.21<br>(0.22)  | 6.1<br>(0.32)  | 6.9<br>(0.35)  | 5.35<br>(0.33) |

clearly FEV1 expressed as % initial is related to the starting FEV1 and as shown in table 3.2 can give very misleading impressions of the degree of reversibility. Nisar et al (1990) have suggested an increase in FEV1 of at least 15 percent and 200ml should be used as the cut off between reversible and irreversible. This value has the advantage of simplicity and is above our 95% confidence intervals for the measurement of FEV1 in this group of patients with severe COPD both within and between days. This is the criteria which has been used to define bronchodilator reversibility in spirometric terms in this thesis.

#### Reversibility to salbutamol

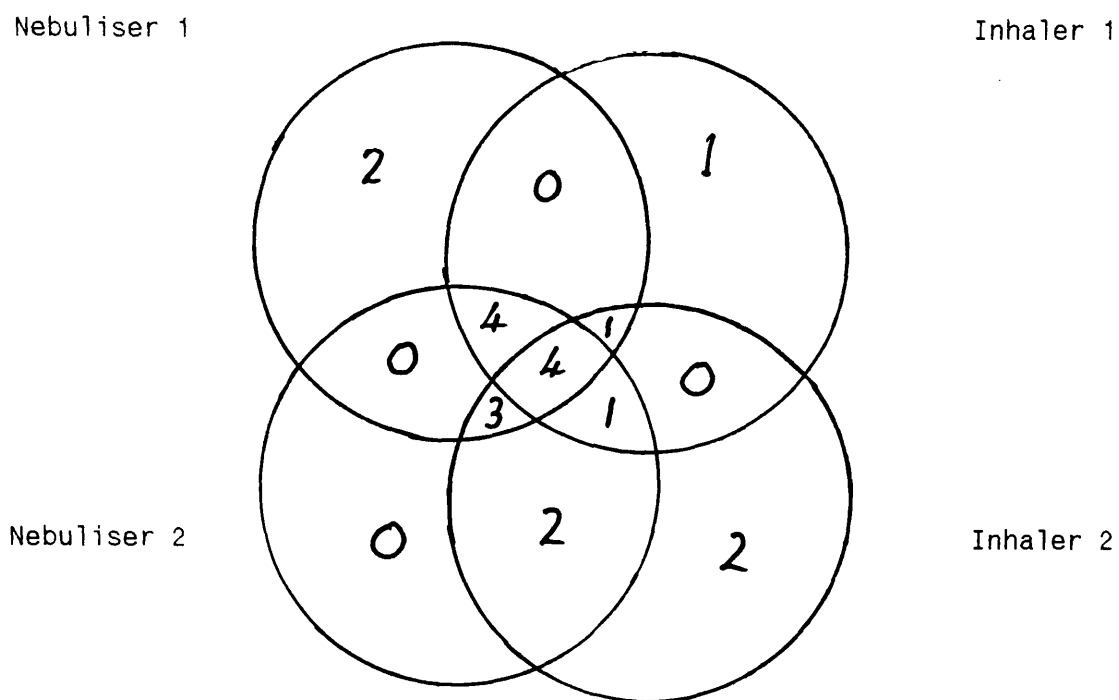
35 subjects were tested for reversibility to salbutamol on 2 separate days prior to commencing the study. Subjects abstained from  $\beta$  agonist inhalers for at least 6 hours, and from anticholinergic inhalers for at least 12 hours prior to the tests. All other medication was continued unchanged. On each occasion reversibility to 200 micrograms inhaled salbutamol (Ventolin, Allen and Hanburys) from a metered dose inhaler and to 5mg nebulised salbutamol (Ventolin, Allen and Hanburys) via an acorn nebuliser and mask (System22) were determined. All FEV1 measurements were performed on a vitalograph wedge spirometer, values quoted are the best of 3 technically acceptable attempts. The interval between administration of inhaler and nebuliser was 15 minutes. Results of these tests are detailed in table 3.2. Additional benefit from the high dose nebulised bronchodilator was small, but statistically significant. The mean additional improvement being 28 and 52mls ( $p < 0.03$  and  $< 0.002$  respectively) on each test day. The relationship between classification of reversibility by FEV1 change with inhaled and nebulised drug on both test days is expressed diagrammatically in the Venn diagram of figure 3.7.



Only 4 subjects increased their FEV1 by at least 200mls more compared to the value after 200micrograms inhaled salbutamol, the largest additional increase was 300ml. No subject showed an additional improvement of greater than 200mls on both tests. (It is not known what the variability of post bronchodilator FEV1 is, nor is it known what additional improvement following high dose nebulised therapy is required to exceed the variability of the measurement. It seems likely that it will be similar to the baseline variability of FEV1) The value for reversibility used subsequently is largest value FEV1 achieved after 5mg nebulised salbutamol. 11 subjects 'reversed' on both test days and 6 on one or other day. The remainder were 'irreversible'. All the subjects who withdrew were from the irreversible group Details of the groups who completed the study are given in table 3.3.

Figure 3.7

Reversibility to 200mcg salbutamol via MDI and  
5mg salbutamol via nebuliser on both test days ( $n=20$ )

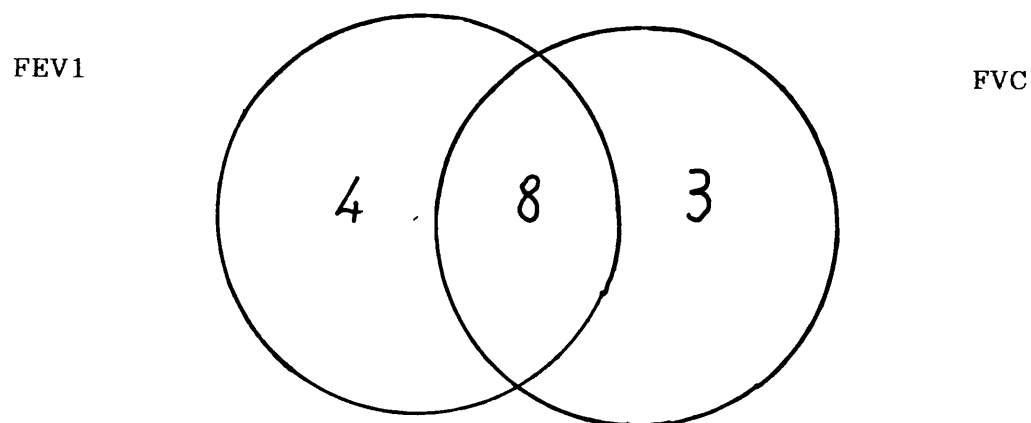


### Reversibility to oxitropium bromide

Reversibility to oxitropium bromide was determined on 2 occasions (on the 2 practice days and on days 3 and 4 of the study). Mean starting FEV<sub>1</sub>(SE) for the whole group was 0.77(0.03)L, rising by 0.17(0.03)L 1 hour after 200micrograms oxitropium bromide( $p<0.001$ ), compared to a small fall of 0.03(0.02)L following the placebo medication( $p<0.05$ ). On days 3 and 4 of the protocol 12 subjects were reversible to oxitropium by FEV<sub>1</sub> criteria and 20 were irreversible. Eight of these 'reversible' subjects increased their FEV<sub>1</sub> by at least 200ml on both occasions it was tested (using data on change in FEV<sub>1</sub> from the 2 training days). Seven other subjects showed a rise in FEV<sub>1</sub> of at least 200mls to oxitropium on one or other of the 2 days it was administered. Details of the lung function of the reversible and irreversible groups from days 3 and 4 of the study are given in table 3.4. Assessing reversibility by changes in FVC (increase in FVC  $\geq$  400ml) rather than FEV<sub>1</sub> did not increase the numbers in the reversible group as shown in figure 3.8. Changes in PEFR moved in the same direction as FEV<sub>1</sub> and FVC.

Figure 3.8

Reversibility to oxitropium defined by  
FEV1 increase > 200ml or FVC increase > 400ml



**Table 3.4** Reversible and irreversible groups defined by increase in FEV1 > 200ml in response to 200mcg oxitropium bromide from a MDI

| [All mean<br>(SE)] | Change in<br>FEV1 (L) | FEV1 (L)       | FVC (L)        | PEFR (L)       | FRC box<br>(L) | TLC box<br>(L) | FRC He<br>(L) |
|--------------------|-----------------------|----------------|----------------|----------------|----------------|----------------|---------------|
| Rev (n=12)         | 0.33<br>(0.04)        | 0.93<br>(0.06) | 2.4<br>(0.17)  | 2.73<br>(0.23) | 6.17<br>(0.43) | 7.65<br>(0.6)  | 5.3<br>(0.35) |
| Irrev (n=20)       | 0.08<br>(0.02)        | 0.68<br>(0.05) | 1.74<br>(0.11) | 2.04<br>(0.19) | 6.0<br>(0.32)  | 6.79<br>(0.36) | 5.1<br>(0.31) |

**Table 3.5** Lung function data grouped by reversibility to both beta agonist and anticholinergic bronchodilators

| mean(SE)    | Reversible to<br>both salbutamol<br>and oxitropium<br>(n = 8) | Irreversible to<br>both salbutamol<br>& oxitropium<br>(n = 11) | Reversible to<br>salbutamol only<br>(n = 9) | Reversible to<br>oxitropium only<br>(n = 4) |
|-------------|---------------------------------------------------------------|----------------------------------------------------------------|---------------------------------------------|---------------------------------------------|
| FEV1 (L)    | 0.95(0.08)                                                    | 0.59(0.06)*                                                    | 0.91(0.11)                                  | 0.78(0.07)                                  |
| FVC (L)     | 2.5(0.2)                                                      | 1.5(0.08)*                                                     | 2.16(0.35)                                  | 2.04(0.63)                                  |
| FRC Box (L) | 6.09(0.64)                                                    | 6.02(0.45)                                                     | 6.31(0.44)                                  | 5.98(0.48)                                  |
| FRC He (L)  | 5.18(0.51)                                                    | 5.28(0.49)                                                     | 5.55(0.37)                                  | 4.88(0.39)                                  |

\*significantly  $p < 0.05$  different from subjects showing reversibility to one or both drugs

#### Relationship between reversibility to salbutamol and to oxitropium.

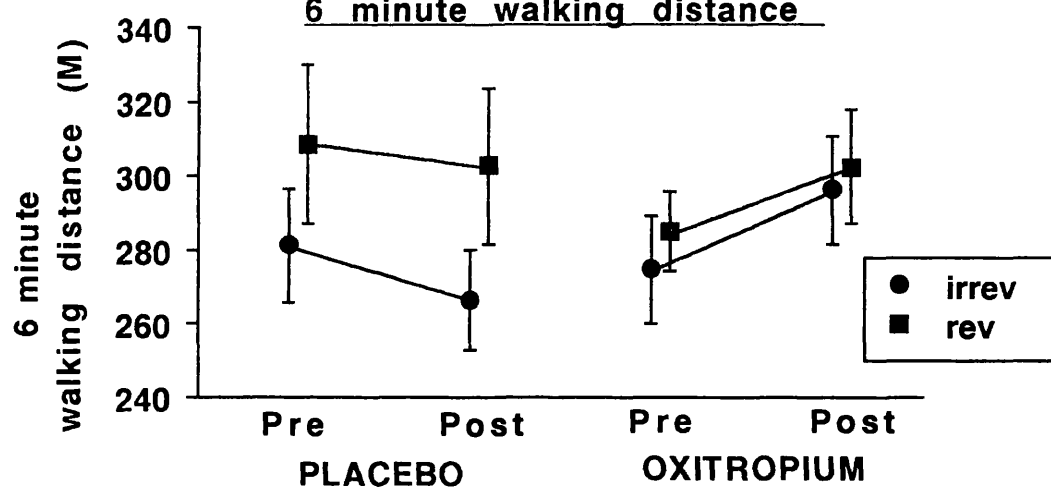
11 of the 32 subjects showed no reversibility to either drug, 8 reversed to both, 9 reversed to salbutamol alone and the remaining 4 subjects only reversed to oxitropium (table 3.5). The group showing no reversibility to either drug had a significantly lower pre bronchodilator FEV1 and FVC compared to those who showed any improvement after either bronchodilator ( $p < 0.001$  for both FEV1 and FVC). There were no significant differences in pre treatment lung volumes between the reversible and irreversible groups measured by either helium dilution or plethysmography. Neither were there any differences between those patients who reversed to the anticholinergic compared to those who reversed to the B agonist. The larger number of patients who reversed to salbutamol alone than placebo may be explained by the method of calculation of salbutamol reversibility, which was from the largest improvement from 2 tests compared to oxitropium reversibility which was the improvement from 1 test. There were no significant differences between the degree of bronchodilatation after 200mcg oxitropium and either 200mcg or 5mg salbutamol when the results of single tests are compared.

#### Relationship between improvement in FEV1 and change in walking distance and breathlessness.

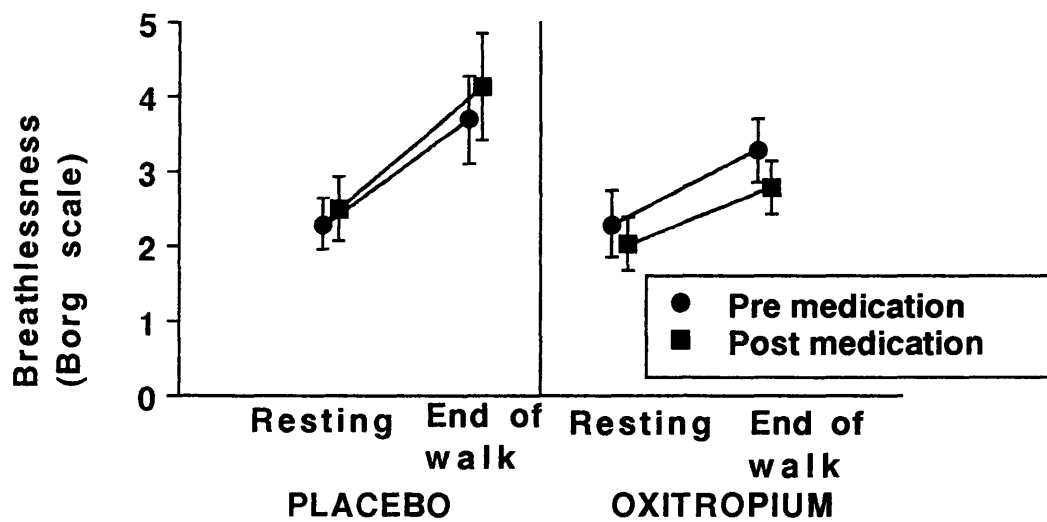
There were no significant differences between the pre drug walking distances in the reversible and irreversible groups (defined by change in FEV1 following 200mcg oxitropium on the test day). The irreversible group walked significantly further after the bronchodilator, the reversible group showed a trend towards improvement in walking distance which failed to reach statistical significance (figure 3.7). There were no significant differences in either resting or final breathlessness scores between the 2

Figure 3.9

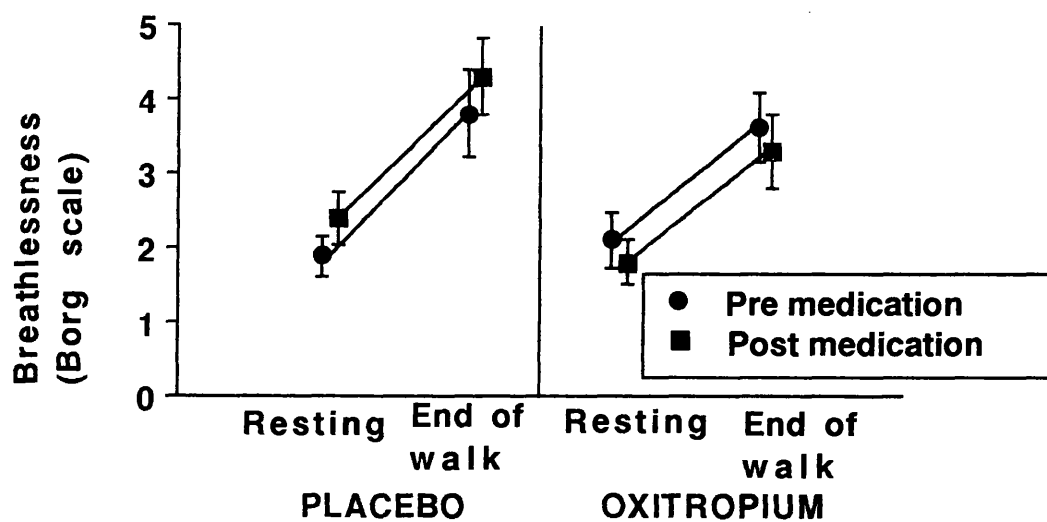
Effect of oxitropium on  
6 minute walking distance



**Figure 3.10** Breathlessness ('reversible subgroup')



**Figure 3.11** Breathlessness ('irreversible subgroup')





groups. Only the irreversible group felt significantly less breathless at rest following the bronchodilator  $p < 0.05$ . Falls in end of walk breathlessness in both groups and resting breathlessness in the reversible group showed a trend towards an improvement in symptoms which failed to reach statistical significance (figures 3.8 and 3.9). There was no relationship between increases in FVC or PEFR and improvements in walking distance or reductions in breathlessness.

### Discussion:

The division into reversible and irreversible categories by an arbitrary cut off point is clearly artificial in view of the variability of the test and the normally distributed nature of bronchodilator reversibility. Equally the value of reversibility testing by changes in spirometry in patients with severe COPD may be questioned. Forced expiratory measurements in these patients are not only dependent on airway calibre, but also upon the loss of lung elastic recoil and altered airway collapsibility (Pare 1991).

### Assessment of reversibility:

Despite their limitations improvements in FEV1 are the usual measure of response to bronchodilators. I have assessed reversibility by changes in FEV1 using a value of 200 ml as the division between reversible and irreversible. This value is rather greater than the 95% confidence intervals for the measurement of FEV1 in this series, but is comparable with values used previously (Tweeddale 1984, 1987, Nisar 1990). The use of a slightly larger threshold will result in some patients with statistically significant improvements in FEV1 following bronchodilator being in the irreversible category. Reclassifying patients reversibility status using the 95% confidence intervals found in this study did not alter the main

finding that people with very small improvements in FEV1 improved their exercise tolerance. There was no advantage in using changes in FVC to assess reversibility, changes in FEV1 and FVC moved in parallel. The measurement of FVC in these patients is subject to similar problems as FEV1 and has the additional problem that the prolonged high intrathoracic pressures produced during the manoeuvre may result in syncope and are in any case distressing for the patient when maximal efforts are obtained. The measurement of slow vital capacity may have some advantages in these circumstances. The measurement of PEFV has no advantages in patients with COPD.

The expression of bronchodilator reversibility in terms of percent change from baseline is the commonest method of expressing reversibility, a change in excess of 15% being a bronchodilator response. Although this method of assessing bronchodilator response increases the number of 'reversible' patients to 20 out of 32, the improvement in exercise performance in the irreversible group was nevertheless twice the reversible group (49m vs 20m). Thus whatever method of expressing reversibility is used the improvement does not relate to changes in functional indices.

Those patients with reversibility to both bronchodilators had a higher FEV1 and FVC than those with no reversibility. The lack of response by those with very poor lung function may suggest that loss of bronchodilator response is a late feature of COPD. However no longitudinal data is available on this subject. Alternatively the pathology of the irreversible group may be different with airflow obstruction being due to greater lung destruction and loss of elastic recoil compared to the reversible group whose airflow obstruction may be more attributable to bronchial wall

thickening - and therefore more susceptible to anticholinergic bronchodilator. If this hypothesis were the case then different degrees of hyperinflation might be seen in the 2 groups, the irreversible being more hyperinflated because of loss of lung elastic recoil. This was not the case, hyperinflation was similar in both groups.

#### The relationship between anticholinergic and beta agonist reversibility:

Oxitropium and salbutamol produced similar degrees of bronchodilatation in these patients. This is in contrast to the work of Gross (1984), Douglas (1979) and Crompton (1968) who have suggested that anticholinergic agents are more effective bronchodilators than beta agonists in COPD while the converse is true in asthma. The difference may be explained by the severity of airflow obstruction in comparison to previous studies with relatively small degrees of improvement in FEV1 even in the most reversible patients. The small additional improvement in FEV1 following high doses of bronchodilators are similar to those of other authors studying similar patient groups (Vathenen 1988 and Corris 1983). Corris showed that these small improvements were accompanied by small improvements in exercise tolerance and suggested that measuring walking distance had no advantage over spirometry. The mean improvement in exercise tolerance was 10m between doses of 400mcg and 1600mcg of salbutamol dry powder. Vathenen in contrast found no improvement in exercise tolerance with higher doses of bronchodilator.

#### The relationship between FEV1, bronchodilator reversibility, exercise performance and breathlessness:

I found a weak relationship between walking distance and FEV1. Previous studies in subjects with diverse degrees of airflow obstruction have shown

variable relationships between spirometric variables and walking distance (McGavin 1976, Vathenen 1988, Knox 1988). No study has demonstrated a strong relationship between spirometry and walking distance.

The lack of relationship between breathlessness and spirometry, and change in breathlessness and improvements in spirometry may reflect both the inadequacies of FEV1 as a measurement of improvement in these patients with severe COPD and be a consequence of patients' variable subjective assessment of their symptoms. FEV1 is by definition a measurement made during a forced manoeuvre when large transpulmonary pressures are generated. These pressures far exceed those required to produce maximal expiratory flow, and because they are large cause expiratory collapse of the airway. Thus flow during a forced manoeuvre is dependent both on airway calibre and on the rigidity of the airway wall. In severe COPD there is loss of the supporting architecture of the conducting airways with increased collapsibility. Alterations in bronchomotor tone may increase airway calibre during tidal breathing when transpulmonary pressures are low, and on exercise when they do not exceed those required for maximum flow, but have little effect on FEV1 where airway collapse is the predominant limiting factor. These alterations in bronchomotor tone may be better measured by changes in airways resistance whose measurement does not generate large transpulmonary pressures.

These data are in agreement with clinical observations which suggest that patients improve symptomatically following bronchodilators and that these changes are often not accompanied by clinically significant improvements in FEV1 or FVC. Other authors have found similar improvements in walking distance with accompanying non significant rises in FEV1 with other bronchodilators (Corris, Conellan and Vathenen with salbutamol, Chrystyn and Mahler with theophyllines). Only Mahler (1985) attempted to measure

improvements in breathlessness accompanying the improvements in exercise performance and these authors only examined resting dyspnoea score, they suggest that the improvement in breathlessness they observed may have been due to improvements in respiratory muscle contractility due to theophyllines. Our data showing improvements in breathlessness with drugs which have no effect on muscle contractility suggest that other factors may be responsible.

In conclusion, in contrast to some other authors I have found that prediction of functional improvements following bronchodilator therapy is difficult using FEV1 or other spirometric criteria alone and that improvements in breathlessness are not closely related to changes in these simple measurements derived from forced manoeuvres.

## THE EFFECT OF OXITROPIUM BROMIDE ON OTHER DERIVATIONS OF THE FLOW VOLUME LOOP, AND ON TIDAL FLOWS.

### Methods

Satisfactory flow volume loop data were obtained on 27 patients: in the remainder some data were lost due to a change in the computer software database after the first 8 patients had completed the study.

All data quoted are from days 3 and 4. The variables quoted are those obtained from the maximal flow volume loop with the largest sum of FEV1 and FVC. Tidal flow data were obtained by manual measurement from the overlaid tidal flow volume loop of the best maximal manoeuvre.

Statistical analysis was by paired Student 't' tests, and Spearman correlation coefficients as appropriate.

### Results

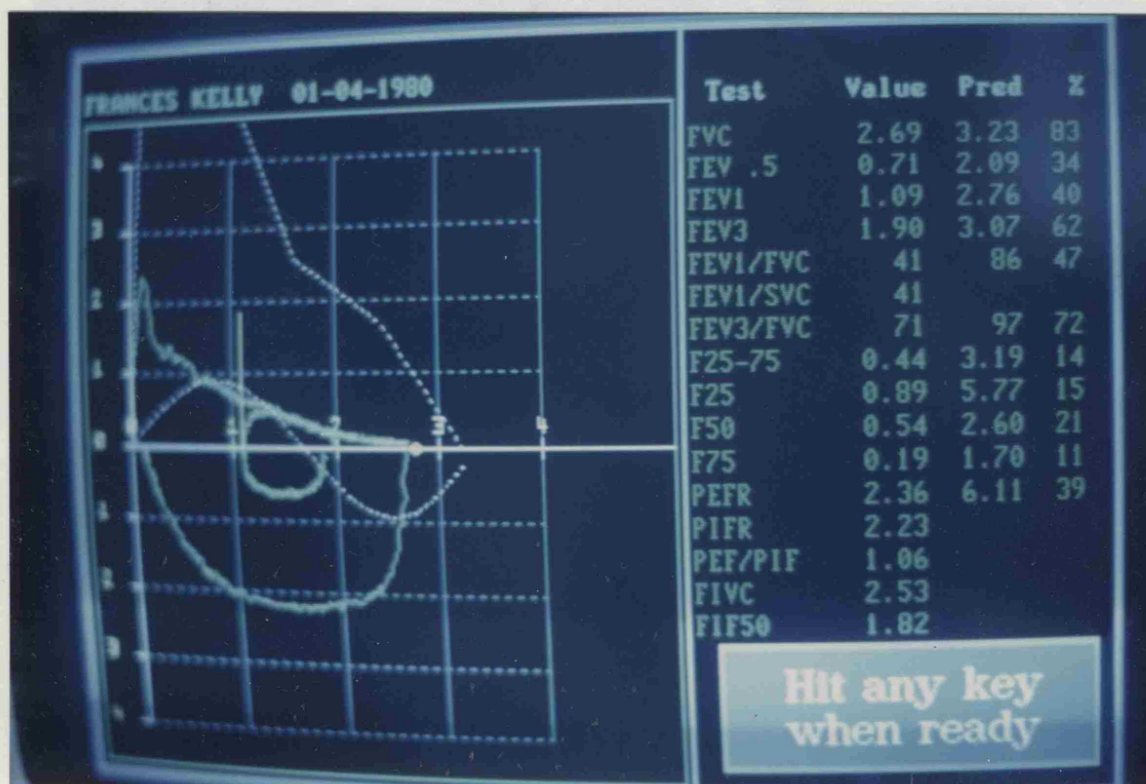
All patients showed the typical flow volume loop appearance of severe COPD with rapid falls in expiratory flows after peak expiratory flow, but with relative preservation of inspiratory flow rates (figures 4.1 and 4.2). The expiratory limb of the tidal flow volume loop lay on or outside the maximum expiratory flow volume loop in all cases, and this relationship was not altered by bronchodilator (figures 4.3 - 4.5).

Between and within day variability of the derivatives of the flow volume loop measurements is summarised in table 4.1).

Only F25 was significantly increased by the administration of bronchodilator. Changes in the mean flow volume loop data are summarised in table 4.2.

Figure 4.1

The pre medication maximal and tidal flow volume loops in a 'reversible' patient

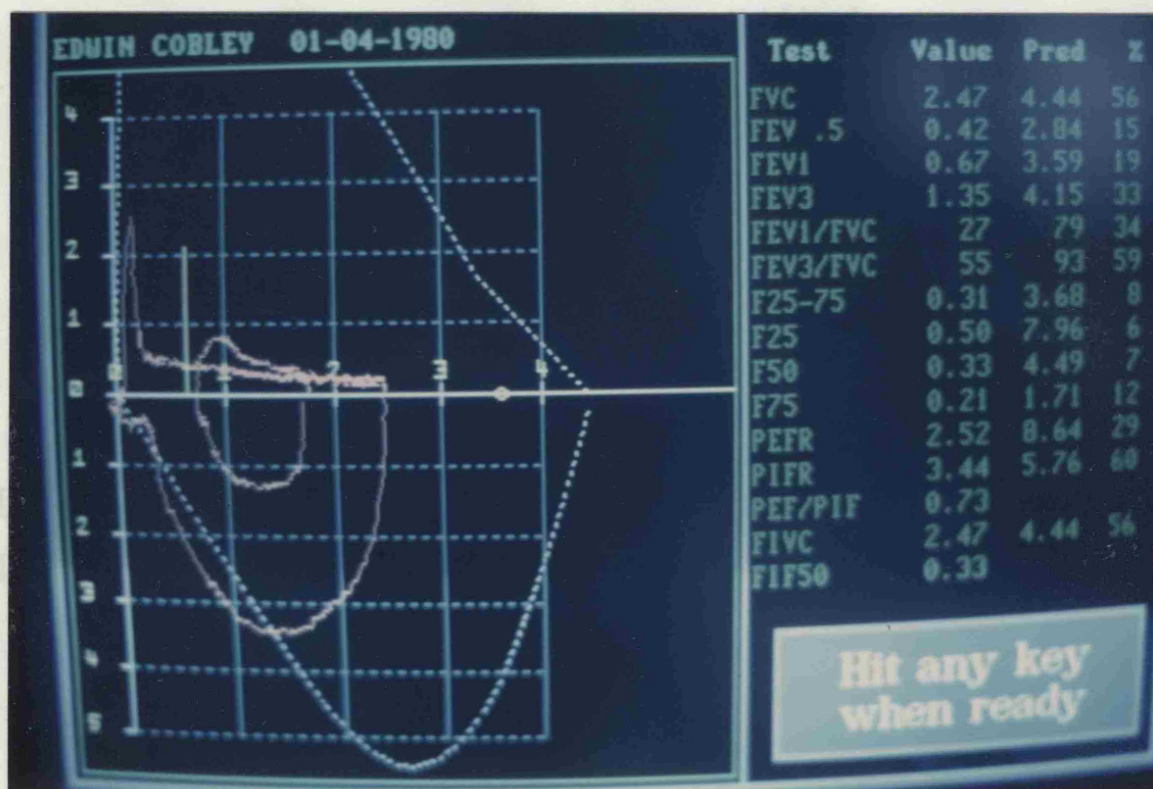


Key to figures 4.1, 4.2, 4.3, 4.4 and 4.5

|          |         |
|----------|---------|
| FVC      | (L)     |
| FEV.5    | (L)     |
| FEV1     | (L)     |
| FEV3     | (L)     |
| FEV1/FVC | (%)     |
| FEV1/SVC | (%)     |
| FEV3/FVC | (%)     |
| F25-75   | (L/sec) |
| F25      | (L/sec) |
| F50      | (L/sec) |
| F75      | (L/sec) |
| PEFR     | (L/sec) |
| PIFR     | (L/sec) |
| PEF/PIF  |         |
| FIVC     | (L)     |
| FIF50    | (L/sec) |

Figure 4.2

The pre medication maximal and tidal flow volume loops in an 'irreversible' patient



|            |            |            |            |            |
|------------|------------|------------|------------|------------|
| F50(L/sec) | 0.54(0.16) | 0.40(0.21) | 0.34(0.13) | 0.33(0.13) |
| F75(L/sec) | 0.17(0.09) | 0.16(0.10) | 0.13(0.06) | 0.17(0.07) |
| F25-75     | 0.09(0.13) | 0.24(0.16) | 0.30(0.14) | 0.38(0.17) |
| (L/sec)    |            |            |            |            |

\* significantly greater than change following placebo  $p < 0.01$



Table 4.1

The within and between day variability of flow volume loop variables  
(Mean difference and standard deviation)

|        | Between day     | Within day      |
|--------|-----------------|-----------------|
|        | Difference (SD) | Difference (SD) |
| F25    | 0.02(0.26)      | 0.07(0.37)      |
| F50    | 0.004(0.08)     | 0.1(0.1)        |
| F75    | 0.01(0.07)      | 0.00(0.06)      |
| F25-75 | 0.00(0.14)      | 0.04(0.12)      |

Table 4.2

The effect of oxitropium bromide on derivatives of the flow volume loop

|                   | oxitropium |              | placebo    |            |
|-------------------|------------|--------------|------------|------------|
| All mean (SD)     | pre        | post         | pre        | post       |
| F25(L/sec)        | 0.68(0.37) | 0.96(0.63)** | 0.66(0.33) | 0.73(0.39) |
| F50(L/sec)        | 0.34(0.16) | 0.40(0.21)   | 0.34(0.13) | 0.33(0.13) |
| F75(L/sec)        | 0.17(0.09) | 0.19(0.10)   | 0.17(0.06) | 0.17(0.08) |
| F25-75<br>(L/sec) | 0.25(0.13) | 0.29(0.16)   | 0.30(0.14) | 0.26(0.13) |

\*\* significantly greater than change following placebo  $p < 0.01$

### Variability of PIF measurements

The variability of inspiratory flow measurements was wide, mean(SD) difference between days was 0.16(0.35)L, and within day 0.18(0.5)L. These values are derived from pre drug values on days 3 and 4, and from the pre and post placebo values. Oxitropium significantly increased peak inspiratory flow rates  $p < 0001$ , the improvement for the group exceeding the variability of the measurement. Larger increases in PIFR occurred in the reversible subgroup of patients (defined by increase in FEV1  $> 200\text{ml}$ s following oxitropium bromide). There was no relationship between improvements in PIFR and increases in walking distance and reductions in resting breathlessness. Increases in peak inspiratory flow rate correlated significantly with reductions in end of walk breathlessness  $r = 0.59$  ( $p < 0.002$ ) (figure 4.6). This relationship remained significant ( $r = 0.41$ ,  $p < 0.05$ ) even when the patient whose change in PIF was extreme was excluded. When the correlations including all data points were checked using non parametric statistics there was no change in the correlation or level of statistical significance. These results are summarised in table 4.3. The results of the tidal flow data is summarised in table 4.4.

### Tidal flows

In this group of patients the expiratory portion of the tidal flow volume loop frequently crossed the expiratory part of the maximum flow volume loop (figures 4.1 and 4.2). Peak tidal flows were not significantly altered by the administration of bronchodilator (table 4.3). No derivative of the tidal flow volume loop either inspiratory or expiratory correlated with walking distance or breathlessness or their improvement following bronchodilator.

Figure 4.3

The post medication maximal and tidal flow volume loops in the same patient as in figure 4.1

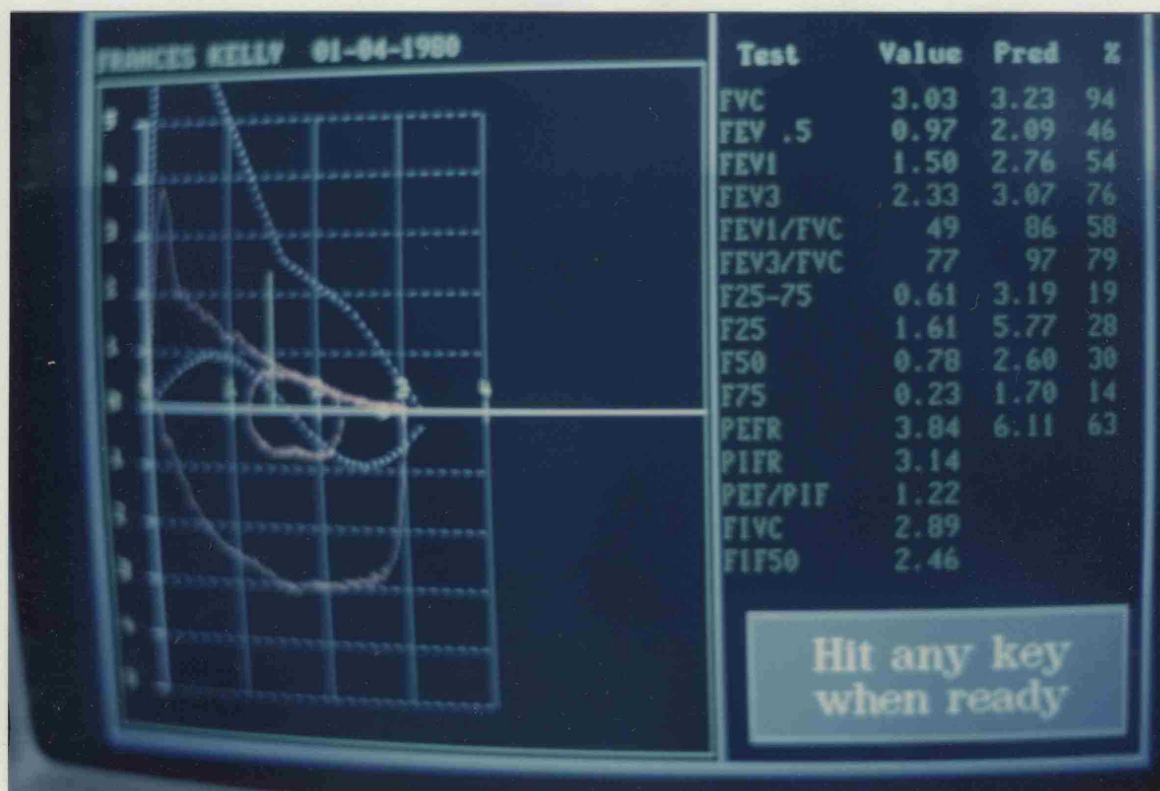


Figure 4.4

The overlaid pre and post medication maximal flow volume loops in a 'reversible' patient

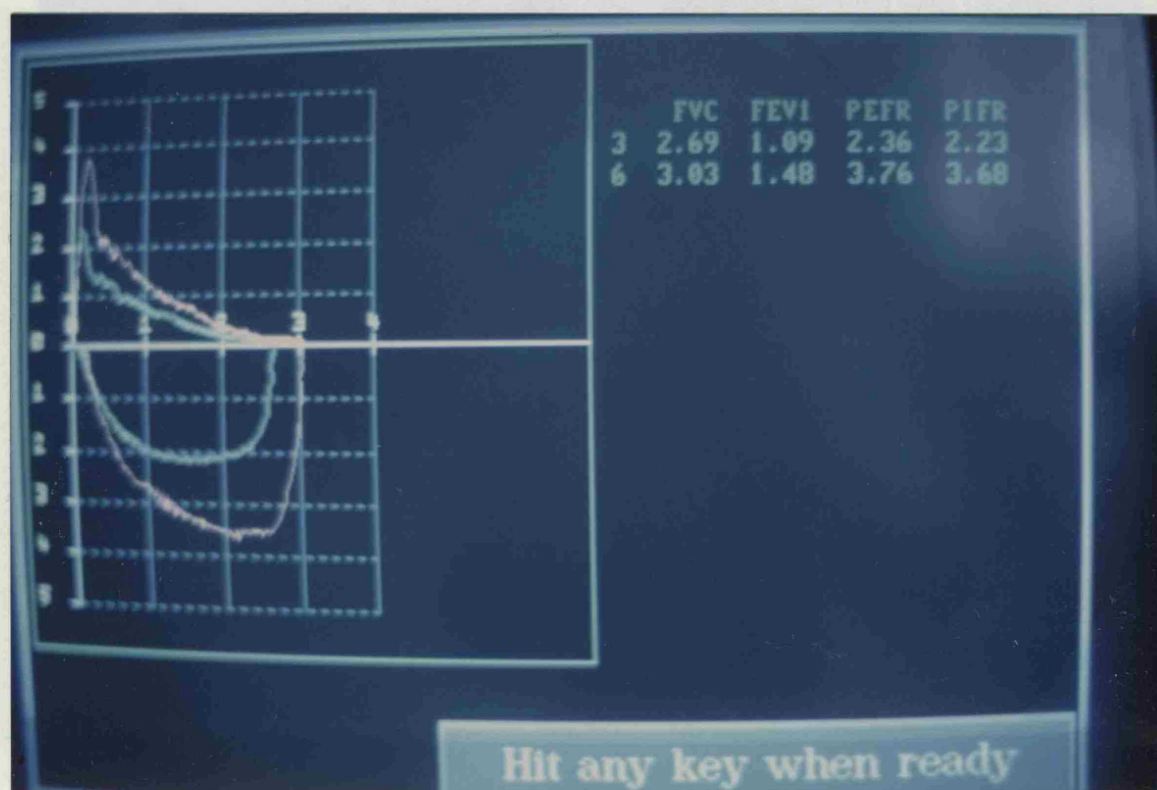
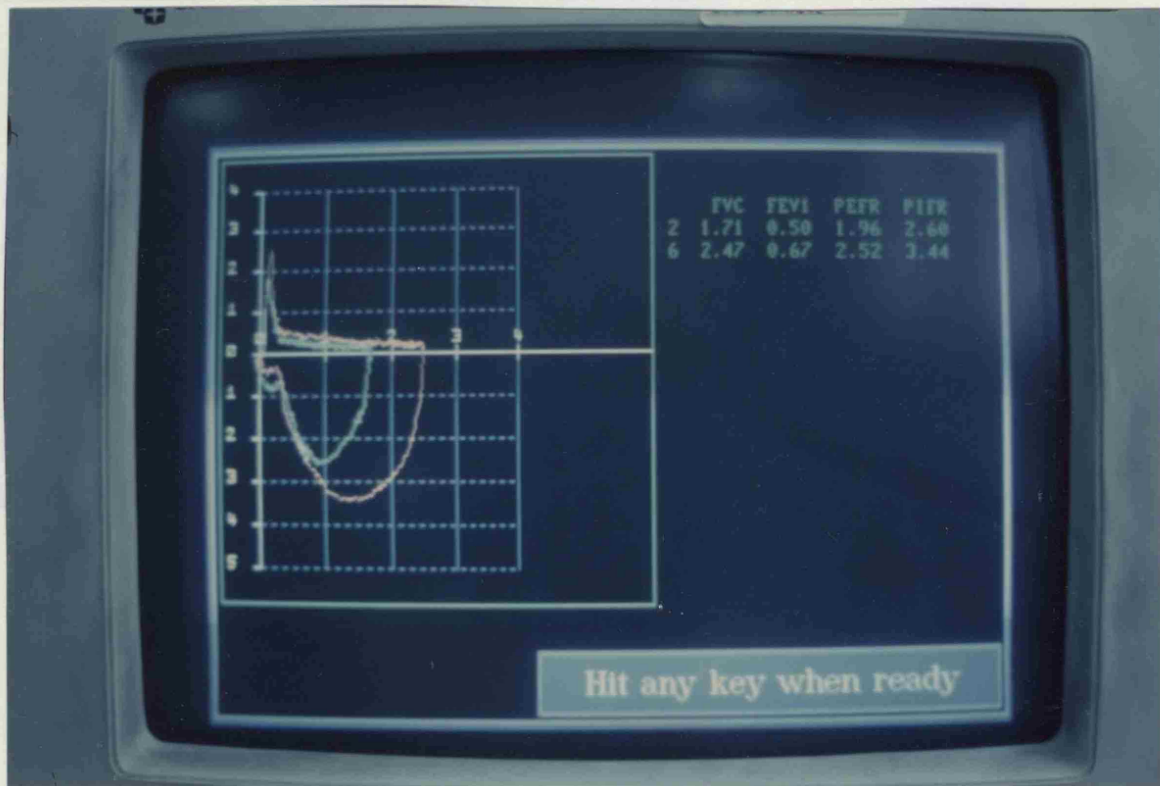


Figure 4.5

The overlaid pre and post medication maximal flow volume loops in an 'irreversible' patient

Table 4.1

The effect of oxitropium bromide on peak inspiratory flows (l/min)



|      |            |            |            |            |
|------|------------|------------|------------|------------|
| Post | 0.95(0.26) | 0.79(0.31) | 1.03(0.32) | 1.61(0.37) |
|------|------------|------------|------------|------------|

**Table 4.3**

**The effect of oxitropium bromide on peak inspiratory flows (L/sec)**

| mean(SD) | Oxitropium   | Placebo    |
|----------|--------------|------------|
| Pre      | 2.27(0.97)   | 2.45(0.87) |
| Post     | 2.64(1.18)** | 2.27(0.91) |

\*\* Significantly different from change with placebo  $p < 0.0001$

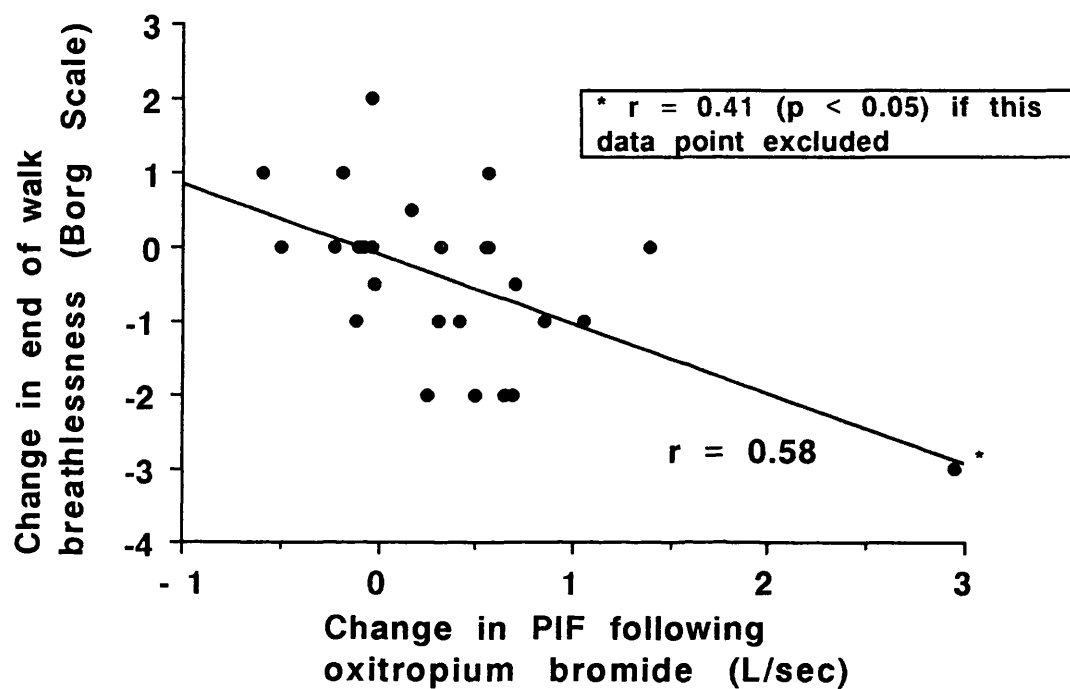
**Table 4.4**

**Effect of oxitropium bromide on peak tidal flow rates (L/sec)**

|          | Expiratory |            | Inspiratory |            |
|----------|------------|------------|-------------|------------|
| mean(SD) | Oxitropium | Placebo    | Oxitropium  | Placebo    |
| Pre      | 0.79(0.23) | 0.77(0.19) | 0.99(0.28)  | 1.02(0.26) |
| Post     | 0.85(0.26) | 0.79(0.31) | 1.03(0.32)  | 1.01(0.37) |

Figure 4.6

Improvement in PIF and  
end of walk breathlessness



## Discussion

Derivatives of the expiratory limb of the flow volume loop provided no additional information in these patients than simple spirometry, only F25 changed following bronchodilator and this was within the variability of the measurement. Those derivatives of the flow volume loop which are said to be effort independent did not change following bronchodilator. However because FVC increased following bronchodilator whilst TLC was unchanged flow at any absolute lung volume was increased (figure 4.4 and 4.5). Thus the use of a flow rate at a proportion of the vital capacity as a measure of response to bronchodilator is inadequate, a more appropriate measure of improvements in flow later in the vital capacity would be the flow rate at a similar absolute lung volume below TLC.

Overlap of the expiratory portions of the tidal and maximal flow volume loops may be explained by thoracic gas compression during the maximal expiratory effort. This results in airflow at the mouth underestimating the change in thoracic volume, and therefore the tidal flow volume loop will be placed incorrectly in relation to the absolute change in lung volume (change in the volume of the air within the thorax rather than volume of gas expired. This artefact could be avoided if instead of measuring expired volume at the mouth the change in thoracic volume were measured using a constant pressure plethysmograph.

While forced expiratory measurements are subject to effort dependent flow limitation due to airway collapse inspiratory flows are not. PIFR is usually regarded as being too effort dependent to be a clinically useful measurement but in this study it increased highly significantly, the improvements correlating with improvements in end of walk breathlessness but not with resting breathlessness. Patients with COPD are unable to



increase expiratory flows in response to exercise without altering their end expiratory lung volume (Stubbing). Increases in ventilation are thus dependent either on dynamic hyperinflation, or on increasing breathing frequency. Increases in PIFR will allow increases in ventilation since inspiratory time may be shortened at a given ventilation. In addition the effort required for a given airflow will be reduced with possible reductions in breathlessness. The increases in PIFR may be due to the reductions in lung volumes following bronchodilator therapy (vide infra) placing the diaphragm at a more advantageous part of its length tension relationship, alternatively increases in bronchial calibre may be important.

The within day variability of the peak inspiratory flow measurements are wider than the between day variability because the measurement is more effort dependent than forced expiratory manoeuvres, and as this was a strenuous protocol the patients were becoming tired towards the end of a testing day. The fall in PIF post placebo may also be explained by this. In conclusion measurement of inspiratory flow rates may be useful in assessing the response to bronchodilators, and is a better correlate of improvements in breathlessness than any expiratory variable.

## THE EFFECT OF NEBULISED SALBUTAMOL ON WALKING DISTANCE AND RESTING BREATHLESSNESS IN COPD

### Introduction

The work described above has shown that improvements in 6 minute walking distance and breathlessness occur in response to inhaled oxitropium bromide, and that this response is independent of change in FEV 1. Berger (1988), Corris (1983) and Connellan (1982) have shown that 12 minute walking distance improves following beta agonist administration and that this improvement in exercise performance is independent of changes in spirometry. However no measurements of symptoms were made. The relationship between improvements in exercise tolerance and breathlessness occurring in response to nebulised Salbutamol, and their relationship to spirometric changes is not well characterised, nor is it known if short term improvements in exercise tolerance and symptoms following bronchodilator are sustained.

### Methods

23 patients (age(SD)63.2(7)years), FEV1 0.9(0.36)L with stable chronic obstructive pulmonary disease were recruited from out patient clinics at Fazakerley Hospital. 22 regularly took inhaled beta agonists, 13 inhaled anticholinergics, 5 were using theophyllines and 16 inhaled steroids. Patients with known cardiac or other respiratory disorders were excluded from the study, as was any patient whose mobility was impaired through musculoskeletal problems. All the patients were aware of the aims of the study but were naive to the methods involved. No attempt was made to exclude patients on the basis of bronchodilator or steroid reversibility.

Each patient attended on 2 occasions at the same time of day one week apart. All were instructed to abstain from oral bronchodilators for 24 hours, from anticholinergic inhalers for 12 hours and from beta agonists aerosols for 6 hours prior to study. Inhaled steroids were continued unchanged throughout the study period. Patients performed one practice 6 minute corridor walk and after a period of rest breathlessness and FEV 1 were measured. Breathlessness was assessed using a modified Borg category scale by asking the question "How breathless do you feel now". FEV 1 was measured on a bellows spirometer (Vitalograph). A 6 minute corridor walk test was then performed: no encouragement was given during the walk, but the aims of the test were stressed. SaO<sub>2</sub> and pulse were measured each minute throughout the walk and for 1 minute after by an ear oximeter (Biox 3700e). The oximeter was carried by a technician who followed the patient during the walk. Patients then received either 5 mg of nebulised Salbutamol or 5 mg normal saline in single blind random order from a System 22 acorn nebuliser driven by 5L O<sub>2</sub> per minute. After 15 minutes rest breathlessness was again assessed and FEV1 measured. A further 6 minute corridor walk was performed with oximetry. After a further 1 hour 45 minutes rest a final assessment of breathlessness and 6 minute corridor walking distance was made.

A sub group of 13 patients took part in both the Salbutamol study and the oxitropium study, and in these we were able to assess the effects of both drugs on breathlessness and walking distance. Statistical analysis was by means of a one way ANOVA to assess the baseline variability in walking distance and FEV 1 and by Students "t" tests for paired data and Wilcoxon signed rank tests to assess changes in walking distance and breathlessness following bronchodilator. While the quoting of the standard error for Borg

Scale breathlessness data is not strictly correct, those values are given to provide an indication of the spread of the data

## Results

There were no significant differences in baseline spirometry, walking distance or breathlessness on either test day. Nebulised Salbutamol produced a statistically significant rise in FEV 1 when measured at both 15 minutes post Salbutamol and 2 hours post Salbutamol whereas nebulised saline had no effect on FEV 1 (table 5.1). Walking distance was improved significantly by the nebulised beta agonist compared to placebo, the difference being 39.5 metres and 48 metres at 15 minutes and two hours respectively. Both of these improvements were highly significant ( $p < 0.001$ ). Resting breathlessness was significantly reduced by Salbutamol compared to placebo at both 15 minutes ( $p < 0.05$ ) and 2 hours post drug ( $p < 0.02$ ).

As with the oxitropium data this data may be divided into reversible and irreversible subgroups using the same criteria as before. Once more this analysis shows that improvement in symptoms and in the walking distance are independent of the change in FEV 1. The results of the experiment are summarised in figures 5.1 and 5.2.

The data from the sub group of 13 patients who took part in both studies is summarised in table 5.2. There were no significant baseline difference between a 6 minute distance, breathlessness or spirometry. Both drugs produced significant improvements in 6 minute distance, there being no significant difference between the improvements produced by either drug. Both drugs produced reductions in resting breathlessness, however only the reduction following Salbutamol administration achieved statistical significance.

**Table 5.1**

**The effect of nebulised salbutamol on walking distance and resting breathlessness**

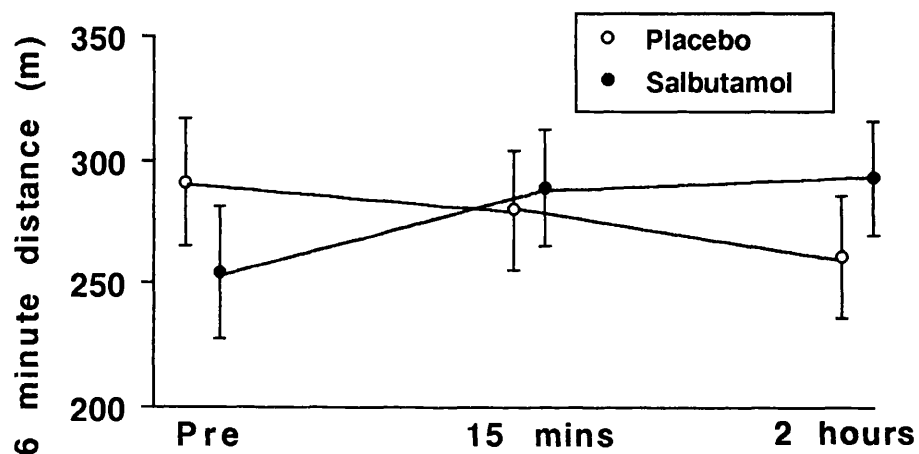
| mean(SE) | Sodium chloride |             |            | Salbutamol |             |            |
|----------|-----------------|-------------|------------|------------|-------------|------------|
|          | FEV1(L)         | 6MD(m)      | Borg       | FEV1(L)    | 6MD(m)      | Borg       |
| Baseline | 0.89(0.07)      | 282.8(16.8) | 3.35(0.40) | 0.90(0.07) | 261.6(16.8) | 2.77(0.30) |
| 15 mins  | 0.87(0.07)      | 272.2(16.8) | 3.23(0.30) | 1.14(0.11) | 290.9(15.7) | 1.85(0.25) |
| 2 hours  | 0.85(0.07)      | 259.7(15.8) | 3.13(0.23) | 1.11(0.10) | 289.6(16.4) | 2.12(0.29) |

**Table 5.2**

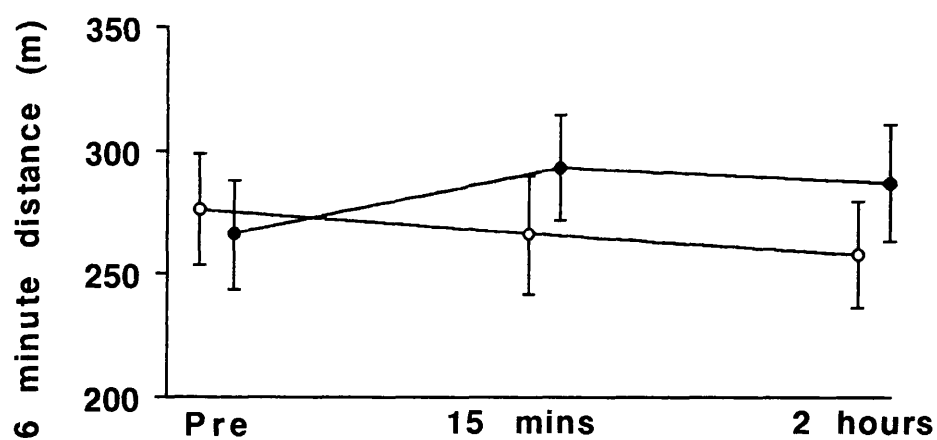
**The effect of nebulised salbutamol and inhaled oxitropium bromide on spirometry, walking distance and resting breathlessness in the 13 individuals who took part in both studies.**

| mean(SE)  | Placebo     | Oxitropium  | 15 mins NaCl | 15 mins salbutamol | 2 hours salbutamol |
|-----------|-------------|-------------|--------------|--------------------|--------------------|
| 6MD pre   | 306.1(14.5) | 290.5(13.3) | 297.2(24.8)  | 269.2(26.7)        | 269.2(26.7)        |
| 6MD post  | 308.5(16.6) | 315.9(12.9) | 282.4(25.9)  | 292.6(23.6)        | 297.1(24.5)        |
| change    | 2.5(9.6)    | 25.4(7.6)   | -14.8(8.2)   | 22.7(8.8)          | 27.9(8.1)          |
| FEV1 pre  | 0.89(0.08)  | 0.85(0.08)  | 0.88(0.11)   | 0.91(0.1)          | 0.91(0.1)          |
| FEV1 post | 0.86(0.08)  | 1.03(0.1)   | 0.88(0.11)   | 1.14(0.13)         | 1.08(0.12)         |
| change    | -0.03(0.03) | 0.18(0.04)  | 0.0(0.03)    | 0.23(0.04)         | 0.18(0.05)         |
| Borg pre  | 2.1(0.3)    | 2.1(0.3)    | 2.9(0.6)     | 2.5(0.5)           | 2.5(0.5)           |
| Borg post | 2.5(0.4)    | 2.1(0.4)    | 3.5(0.5)     | 1.8(0.3)           | 1.96(0.4)          |
| change    | 0.3(0.2)    | 0.0(0.3)    | 0.6(0.5)     | -0.7(0.4)          | -0.5(0.4)          |

**Figure 5.1**    Irreversible patients response to salbutamol



**Figure 5.2**    Reversible patients response to salbutamol



## Discussion

These data show that an improvement in 6 minute walking distance and breathlessness independent of changes in FEV 1 occurs 15 minutes after administration of 5 mg of nebulised Salbutamol, and that the improvement is sustained for at least 2 hours post administration. The improvements observed together with the results from the study of the effect of oxitropium bromide, demonstrate that those without clinically significant spirometric improvement improve at least as much in functional terms as those with larger changes in FEV 1. The similar findings following administration of both classes of drugs confirm that the mechanism of improvement in breathlessness and walking distance is an alteration in lung mechanics brought about by both agents rather than a specific effect on lung receptors or muscle fatigue as has been suggested to explain improvements in exercise tolerance following theophylline administration (Chrystyn 1988, Mahler 1983).

Similar improvements in walking distance occurred following both 200 micrograms of oxitropium and 5 mg of Salbutamol suggesting that both agents are producing similar alterations in lung mechanics despite a higher FEV1 following salbutamol administration. This raises questions regarding the need for high doses of nebulised bronchodilators in COPD particularly when assessment is based solely on changes in spirometry. Several other studies have also addressed the question of high dose nebulised bronchodilators in COPD, and they found no sustained benefit from the nebulised route of administration compared to the metered dose inhaler ( Gunewardena 1988, Allen 1988 and Jenkins 1987) The improvements in walking distance following Salbutamol administration are in agreement with previous work by Berger (1988), Corris (1983) and Vathenen (1988). However the work of Vathenen was complicated by an excessive placebo response as large as that

obtained following the active drug together with a complex design and a learning effect. Both Corris and Vathenen demonstrated that higher doses of bronchodilator produced a slight additional rise in FEV 1.

The duration of improvement in breathlessness and exercise performance following salbutamol administration is not clear. The studies by Vathenen and Corris found that the improvements measured at 1 hour had declined somewhat at 4 hours post drug. This study shows there is continued improvement 2 hours after drug administration. The reason for the further improvement is not clear, but may be related to resolving of short lived VQ imbalance caused by the bronchodilator (Vide infra) The results of these experiments and previous comparisons between nebulisers and metered dose inhalers emphasises the need for careful assessment of patients including functional and symptomatic assessment if possible before the prescription of nebulised therapy. These studies suggest that we should be more willing to believe our patients' assessment of the effects of bronchodilators rather than relying on limited tests of pulmonary function such as FEV1, FVC and PEFr.

Both the oxitropium and salbutamol experiments have shown that improvements in breathlessness and exercise tolerance are not confined to those with spirometric changes or to any particular class of drugs. Changes in lung volumes, airways resistance and breathing pattern may more closely reflect changes in breathlessness, and may help predict those who will derive functional benefit from bronchodilators. The changes in these variables and their relationship to changes in breathlessness has only been studied in response to inhaled oxitropium bromide.



## LUNG VOLUME MEASUREMENTS

### Plethysmographic measurements

The measurement of plethysmographic lung volumes in the presence of airflow obstruction has several potential flaws which have been considered in historical review of the technique.

The plethysmographic method of lung volume estimations was first described in principle by Pflüger in 1882. However the method was discarded by investigators as being too unreliable for clinical or physiological use. In the 1940s and the early 1950s lung volume estimations focused on the rapid decompression method described by Hitchcock (1946) and Dejours (1953). In this method the pressure about the body and in the trachea and lungs is increased equally above atmospheric thereby increasing the number of molecules of gas within the lungs. The pressure is rapidly released, and the amount of gas flowing out of the lungs measured. By application of Boyles law the volume of gas in the lungs at atmospheric pressure can be calculated.

Interest in the voluntary compression/decompression method first described by Pflüger was reawakened by Dubois (1955) who with the benefit of better pressure transducers and recording equipment produced a practical system for the measurement of lung volumes. He described an airtight chamber which enclosed the subject who breathed through a mouthpiece with a shutter attached. The shutter occluded the airway and the subject made respiratory efforts against the occlusion. Pressure was recorded at the mouthpiece and in the airtight chamber and by application of Boyles law, with knowledge of the 2 pressures, the volume of gas within the lungs could be calculated as detailed below:-

Boyles law states:

$$PV=K \text{ or } P_1V_1= (P_1+\Delta P)(P_2+\Delta P)$$

rearranging

$$P_1V_1+V_1\Delta P+\Delta V\Delta P=0$$

therefore

$$V_1=\Delta V\Delta P(P_1+\Delta P)$$

when  $\Delta P$  is small and  $P_1$  large then  $P_1+\Delta P$  approaches  $P_1$ (atmospheric pressure)

therefore

$$V_1=-P_1(\Delta V)/\Delta P$$

ignoring the sign

$$V_1 = (\text{atmospheric pressure} - \text{water vapour pressure})(\Delta P/\Delta V)$$

mouth pressure is plotted against box pressure and the slope of this plot

( $\alpha$ ) represents change in mouth pressure per unit change in box pressure.

Therefore to derive the thoracic gas volume (TGV):

$$TGV= \frac{(\text{Atmospheric pressure} - \text{water vapour pressure}) * \text{box calibration}}{\tan \alpha * \text{mouth pressure calibration}}$$

In his original description of the method Dubois describes 2 types of manoeuvre for lung volume estimation in the plethysmograph; a normal inspiration against the shutter until the occlusion is sensed or rhythmic panting efforts against the closed shutter. Dubois recognised that the presence of abdominal gas which is also subject to the compressive/decompressive forces may confound the measurement. However he calculated the average volume of gas in the abdomen to be only 160mls. Bedell et al (1956) first described the use of the plethysmograph to determine what they describe as 'the volume of gas trapped within the lungs'. They measured the difference between FRC by helium dilution and FRC by plethysmography in a variety of clinical situations including 9 subjects

with emphysema, and found the mean difference between the measurements was 1.09L.

Since its first description others have made modifications to the system. Mead (1960) described the volume displacement plethysmograph, which measured changes in volume within the box by means of a Krogh spirometer rather than changes in pressure. The advantage of the modification was that it was better able to measure slow thoracic volume changes such as a vital capacity, the disadvantage was that it had a more limited frequency response. Stanescu (1971) described the pressure corrected flow box, which substituted the integrated flow signal from a pneumotachograph for the spirometer, and thus overcame some of the problems of the limited frequency response.

The method of lung volume estimation by plethysmography was universally accepted without question until the 1970s when problems with the measurement of TLC in acute asthma were recognised. Habib and Engel (1978) showed that measured VTG could vary with different panting techniques. They found that when panting was mainly diaphragmatic the values of TGV were lower than those measured with a mainly intercostal method of panting. This was explained by the authors as the influence of abdominal gas being greater than had hitherto been realised. Brown et al (1978) observed that derived TLC values were higher during induced bronchoconstriction when the panting volume was near to RV compared to measurements performed when panting near to TLC. They postulated that alveolar pressure swings may be nonhomogenous during bronchoconstriction, and that mouth pressure may underestimate alveolar pressure, thus causing an overestimate of lung volumes.

Brown (1980) demonstrated in the dog pressure that at the airway opening underestimated airway pressure when the right lower lobe bronchus was

occluded by a balloon, the underestimate being 8% and suggested that this over estimate was due to inhomogeneous alveolar pressure changes. These findings have not been confirmed in man. Rodenstein et al (1983) showed that inflation of a balloon to occlude the bronchus intermedius made no difference to the TGV measured using mouth pressure in healthy male volunteers.

Stanescu et al (1982) and Shore et al (1982) in a series of experiments showed that TGV derived from oesophageal pressure exceeded that derived from mouth pressure in the presence of induced bronchoconstriction. The magnitude of the overestimate was dependent on the distensibility of the extrathoracic airway, and the degree of airflow obstruction. Rodenstein et al (1982) showed that bypassing the extrathoracic airway with an endotracheal tube abolished the TGV overestimate induced by an artificial airway stenosis caused by inflating a balloon to partially occlude the lower trachea.

Rodenstein and Stanescu (1982) then went on to examine the effect of different panting frequencies on the estimation of TGV in asthmatics and normal volunteers. They found that during pharmacologically induced airflow obstruction in asthmatics TGV derived from oesophageal pressure was similar to that derived from mouth pressure at low (less than 1Hz) panting frequencies, but that the oesophageal pressure exceeded mouth pressure at higher panting frequencies resulting in spuriously high measurements of TGV. There was no difference between oesophageal and mouth pressure in normal volunteers at any panting frequency. Brown (1984) found that frequency dependence also applied to oesophageal pressure measurements used for TGV estimates, and that it was directly proportional to the degree of airflow obstruction. Begin (1984) found similar frequency dependent rises in VTG in COPD, and found that failure to support the cheeks during a

measurement resulted in even higher lung volume estimations in those with the highest airways resistances. The magnitude of the overestimate in this study was small, rarely greater than 2%.

Thus the plethysmographic measurement of lung volume in the presence of airflow obstruction is not straightforward, and has the potential for a number of artefactual errors. I have examined the role of some of these factors in patients with severe COPD (see method validation experiments in the appendix to this thesis), and also related changes in lung volumes to alterations in breathlessness and exercise performance.

## The effect of oxitropium bromide on plethysmographic lung volume measurements

### Introduction

Changes in spirometry have been shown to be a poor guide to the alterations in lung mechanics following bronchodilators which result in a reduced perception of breathlessness. Measurement of changes in lung volume which alter the geometry and improve the efficiency of the respiratory musculature may be more closely related to changes in perceived breathlessness.

### Methods

The methods used in the measurement of plethysmographic lung volumes are detailed earlier. Statistical analysis was by Student paired t tests or Wilcoxon signed rank tests, and by calculating Spearman and Pearson correlations as appropriate.

### Results

Within and between day variability of the body box measurements was good, the coefficient of variation of FRC being 3.4% and 3.5% within and between days respectively (figure 6.1).

For the group as a whole FRC fell following bronchodilator ( $p < 0.01$ ).

There was no change in total lung capacity, while RV fell significantly compared to placebo changes ( $p < 0.01$ ) (table 6.1)

Plethysmographic lung volume measurements were higher than those measured by the helium dilution technique (figure 6.2). Helium dilution and body box measurements for the whole group moved in the same direction following bronchodilator, (change in FRC He -0.25L; change in FRC box -0.27L).

Figure 6.1

Between day variability of  
plethysmographic lung volumes

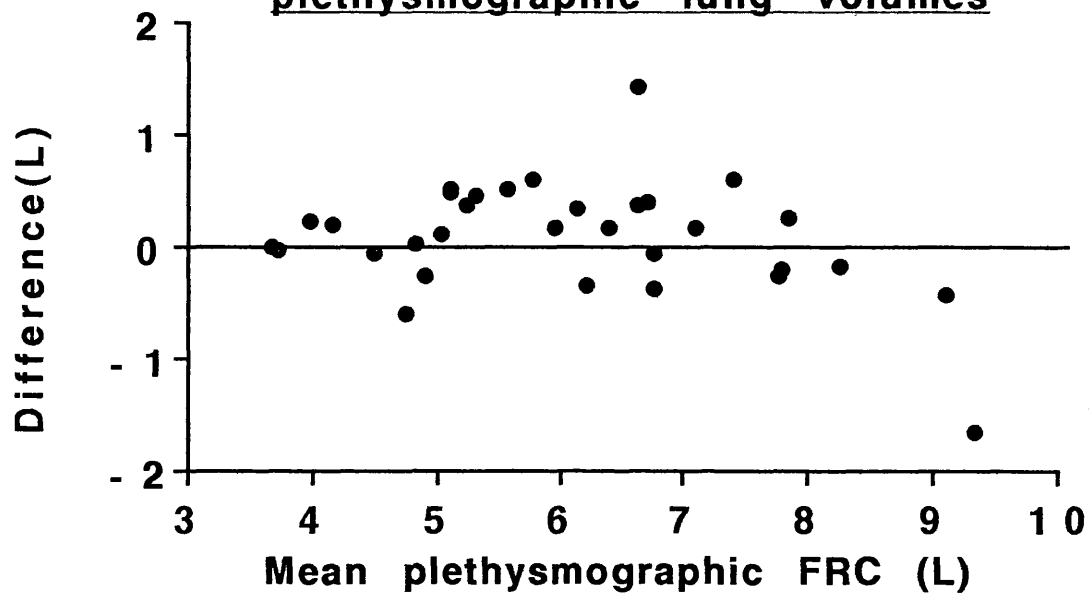


Figure 6.2

Difference between Box and Helium  
FRC measurements

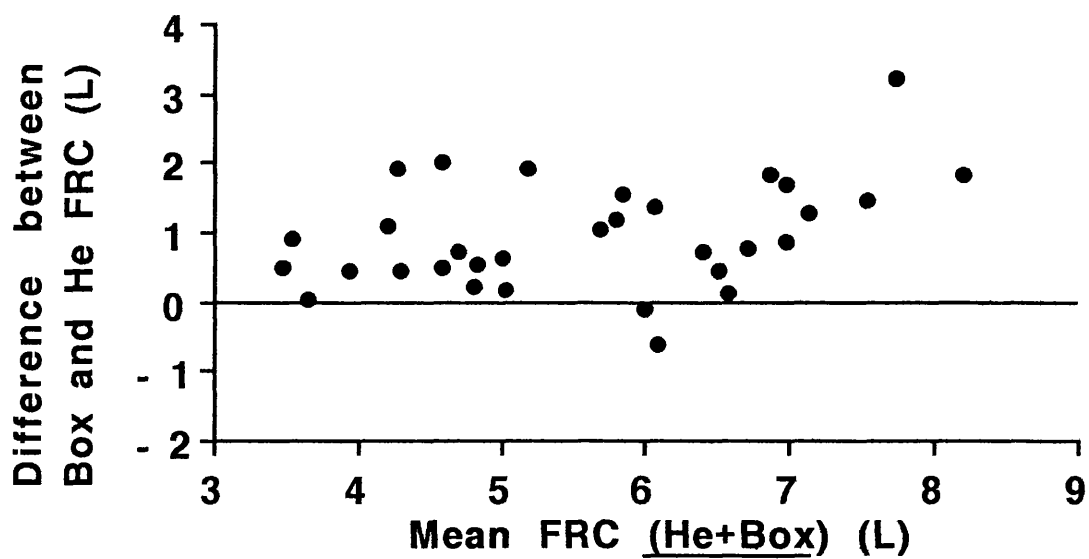


Table 6.1

Changes in plethysmographic lung volumes following placebo and oxitropium

| All mean(SD) | Placebo    |            | Oxitropium |            |
|--------------|------------|------------|------------|------------|
|              | Pre        | Post       | Pre        | Post       |
| TLC(L)       | 7.04(1.89) | 7.18(1.99) | 7.03(1.83) | 7.01(1.77) |
| FRC(L)       | 6.09(1.60) | 6.15(1.58) | 6.06(1.43) | 5.80(1.38) |
| RV(L)        | 5.02(1.60) | 5.28(1.7)  | 5.11(1.52) | 4.75(1.47) |

Table 6.2

Changes in plethysmographic FRC (L) following placebo and oxitropium in reversible and irreversible groups

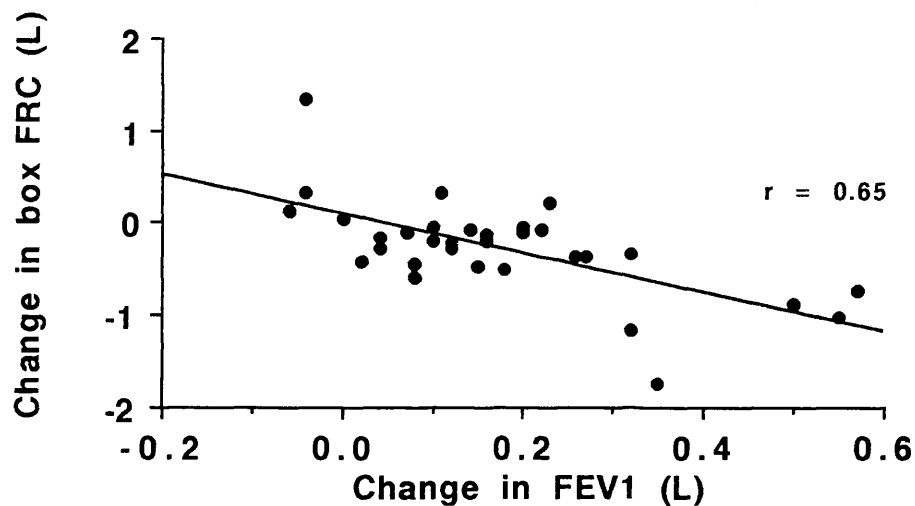
| All mean(SD)   | Placebo    |            | Oxitropium |            |
|----------------|------------|------------|------------|------------|
|                | Pre        | Post       | Pre        | Post       |
| 'Reversible'   | 6.48(0.55) | 6.41(0.46) | 6.17(0.43) | 5.62(0.4)  |
| 'Irreversible' | 5.86(0.31) | 6.00(0.35) | 6.00(0.32) | 5.91(0.31) |



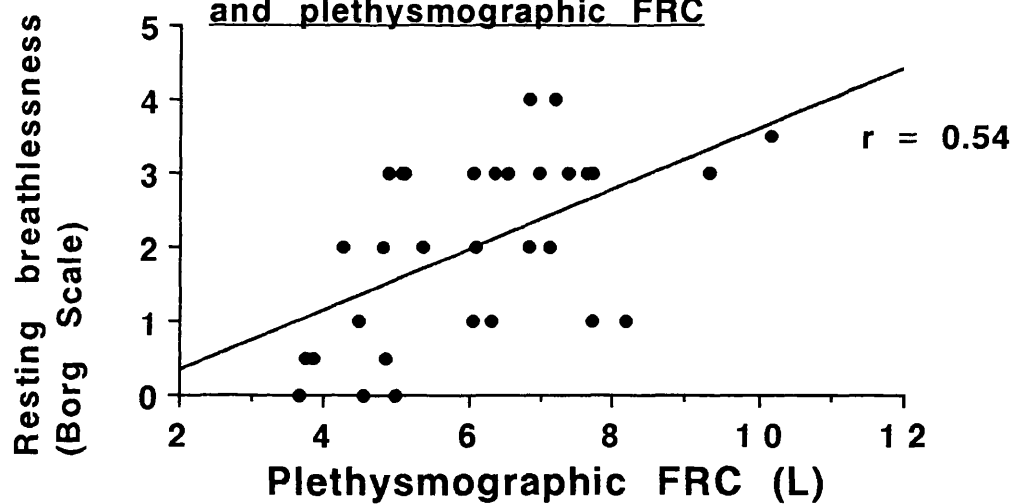
However there was no correlation between the changes in lung volumes measured by helium dilution and plethysmography for individual subjects following administration of oxitropium bromide. Dividing the data into reversible and irreversible subgroups (by change in FEV1 >200mls with bronchodilator) reveals that significant changes in FRC are confined to the subgroup which showed a change in FEV1 >200mls with oxitropium bromide (table 6.2). The group whose FEV1 did not change by >200ml showed trends in the same direction, but these failed to reach statistical significance. The change in box FRC correlated with the change in FEV1 following bronchodilator  $r=0.65$   $p < 0.0001$  (figure 6.3)

Box FRC correlated with resting breathlessness on both test days,  $r=0.48$  and  $0.54$  (figure 6.4), but only correlated with end of walk breathlessness on one of the two days  $r=0.49$ . Percent predicted FRC correlated with resting breathlessness  $r=0.38$  and  $0.54$  ( $p < 0.05$  and  $p < 0.002$  respectively) and with final breathlessness on one day only  $R=0.37$  ( $p < 0.05$ ). There was no correlation between FRC or percent predicted FRC and walking distance.

**Figure 6.3** Relationship between change in FEV1 and change in box FRC with oxitropium



**Figure 6.4** The relationship between breathlessness and plethysmographic FRC



## Changes in helium dilution lung volumes following oxitropium bromide.

### Introduction

Measurements of lung volume made by the helium dilution technique depend for their accuracy on the communication of the intrathoracic airspaces with the mouth. In COPD the helium dilution method may underestimate lung volumes because of very slowly emptying spaces.

Changes in helium dilution lung volumes following bronchodilator may reflect 'true' changes in lung volume, or alternatively may represent changes in the ventilation of slowly emptying air spaces and thus be artefactual, but reflect an increase in the volume of the air communicating with the airway opening. Woolcock (1971) reported falls in lung volume measured by helium dilution in a group of patients recovering from acute asthma. Chrystyn et al (1988) reported increases in FRC and TLC measured by helium dilution in a group of patients with COPD treated with theophylline. I have examined the reproducibility of helium dilution lung volume measurements both within and between days, and related them to changes in 6 minute walking distance and breathlessness both before and after bronchodilator.

### Methods

Details of the methods used for determination of helium dilution lung volumes are given earlier in this thesis.

Statistical analysis was by paired Student 't' tests and Pearson and Spearman correlation coefficients as appropriate.

## Results

There were no significant differences between the first and second measurements of a pair confirming that 15 minutes between measurements is sufficient time to allow for dispersal of helium from slowly emptying spaces of the lung. (table 6.3)

The coefficient of variation for all the helium dilution measurements was good, both within and between days (table 6.4, figure 6.5)

There were no significant differences between the pre drug values either between days three and four, or between the groups when divided into pre placebo and pre oxitropium.

All subjects had elevated lung volumes compared to predicted values in keeping with COPD. The degree of hyperinflation expressed as percent predicted FRC correlated weakly with airflow obstruction (percent predicted FEV1) before medication ( $r = -0.46$ ,  $p < 0.01$ ) There was no correlation between percent predicted TLC and percent predicted FEV1.

There was no correlation between FRC or % predicted FRC and walking distance on either day. FRC correlated with resting breathlessness score on both test days ( $r = 0.41$ ,  $p < 0.02$  and  $r = 0.46$ ,  $p < 0.01$ ) but not with end of walk breathlessness. There was no correlation between percent predicted FRC and breathlessness.

Changes in helium dilution lung volumes following oxitropium bromide.

Helium dilution FRC increased significantly following the placebo inhaler. After oxitropium bromide FRC and RV fell significantly ( $p < 0.01$  and  $p < 0.005$  respectively)(table 6.5). There was no change in TLC following either oxitropium bromide or placebo. Statistically significant falls in FRC and RV were confined to the group whose FEV1 changed by  $>200\text{mls}$  following oxitropium, The changes in the 'irreversible' group showed trends in the same direction but they did not reach statistical significance (table 6.6). There was no correlation between the change in lung volume measured by the helium dilution technique and the changes in either walking distance or breathlessness.

Figure 6.5

The between day variability of helium dilution lung volume measurements

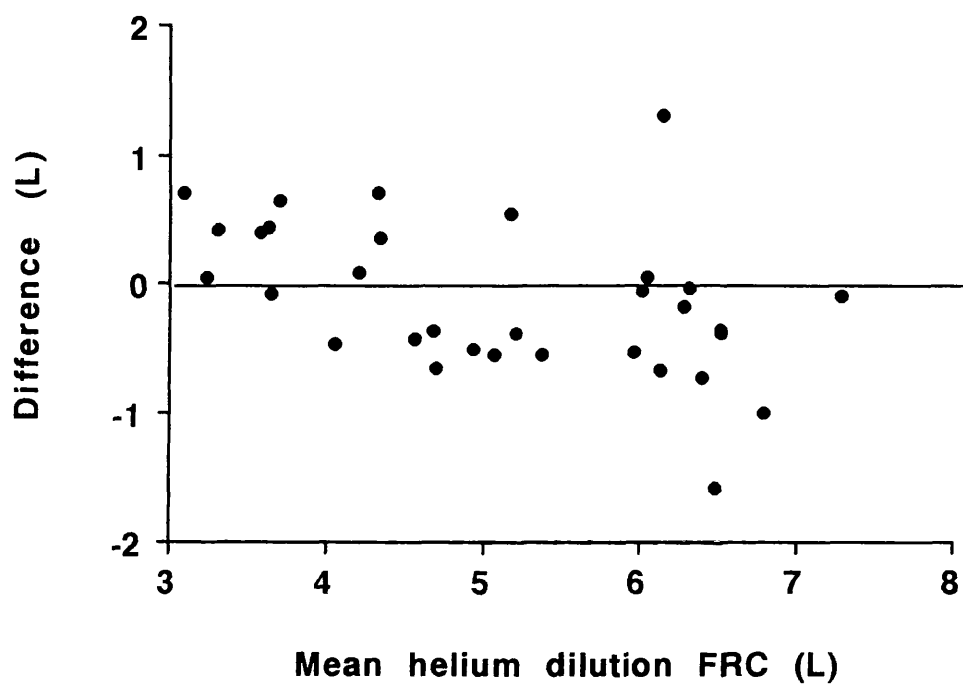


Table 6.3

The helium dilution FRC measurements derived from the first and second from each of a pair of measurements

| All mean (SE) | Day 3 (1)  | Day 3 (2)  | Day 4 (1)  | Day 4 (2)  |
|---------------|------------|------------|------------|------------|
| FRC (L)       | 5.12(0.24) | 5.02(0.23) | 5.05(0.28) | 5.04(0.28) |

All are pre drug values

Table 6.4

The coefficients of variation of the helium dilution lung volume measurements

|     | Between pair of measurements | Within day | Between day |
|-----|------------------------------|------------|-------------|
| TLC | 5.7%                         | 3.8%       | 4.8%        |
| FRC | 6.6%                         | 5.7%       | 5%          |
| RV  | 8.8%                         | 6.6%       | 7.3%        |

Table 6.5

Changes in helium dilution lung volumes following placebo and oxitropium

|               | Placebo    |            | Oxitropium |              |
|---------------|------------|------------|------------|--------------|
| All mean (SE) | Pre        | Post       | Pre        | Post         |
| TLC (L)       | 6.53(0.3)  | 6.44(0.33) | 6.39(0.32) | 6.41(0.27)   |
| FRC(L)        | 5.06(0.21) | 5.28(0.23) | 5.18(0.23) | 4.93(0.23)*  |
| RV(L)         | 4.28(0.23) | 4.24(0.29) | 4.22(0.27) | 3.93(0.22)** |

\*significantly different from placebo value  $p < 0.01$

\*\*significantly different from placebo value  $p < 0.005$

Table 6.6

Changes in helium dilution FRC following oxitropium and placebo

|              | 'Reversible' |            | 'Irreversible' |            |
|--------------|--------------|------------|----------------|------------|
| All mean(SE) | Oxitropium   | Placebo    | Oxitropium     | Placebo    |
| Pre FRC (L)  | 5.3(0.35)    | 5.17(0.33) | 5.1(0.31)      | 4.99(0.28) |
| Post FRC (L) | 4.92(0.36)   | 5.45(0.43) | 4.93(0.31)     | 5.18(0.32) |



## Discussion

The reproducibility of both box and helium dilution lung volume measurements in this series was good. Helium dilution lung volume measurements variability was similar to accepted values (Clausen). The reproducibility of the plethysmographic lung volume measurements in these severe COPD patients was excellent, and was comparable with the quoted reproducibility in normal subjects (Dubois 1956, Clausen). The quality of reproducibility of box volume measurements may be the result of the new computer algorithms, or be a reflection of the careful tutoring of patients to produce 'closed' loops and maintain constant panting frequencies. In obstructive lung disease lung volumes are higher by plethysmography than by helium dilution (Chrystyn 1988, Brown 1978, Mungall 1979 and Woolcock 1971). In this series the magnitude of the difference (1L) was less than in previous published work (Chrystyn reported a mean difference of 1.9L, and Mungall 1.56L). This difference may reflect the effort made to maintain low panting frequencies of 1Hz during the lung volume measurements in the body plethysmograph and thus minimise artefactual overestimates. The residual difference of 1L between box and helium measurements may be due to a combination of factors;

- a) true 'trapped gas' ie areas of the lung which are not in direct communication with the airway opening but are kept inflated by collateral diffusion of gas from adjacent alveoli.
- b) Abdominal gas artefact
- c) The effect of a compliant upper airway (discussed in the method validation experiments in the appendix)
- d) True differences in end expiratory position caused by the differing postures adopted for each measurement.

Abdominal gas artefact and upper airway compliance will account for around 400ml of the difference (Dubois (1956) and work reported in the appendix to this thesis), thus the remaining difference due to other factors is 600ml. It should be noted that the difference between inspiratory capacities between the helium dilution and plethysmographic techniques was in the order of 600 ml. It is therefore possible that the 2 techniques measure the 'true' lung volume in each case and that the remaining difference is due to differences in end expiratory position caused by differing postures during the measurement.

The degree of elevation of FRC and TLC is in keeping with the values found by Chrystyn et al and Mungall et al. The falls in FRC (measured by 2 methods) following administration of bronchodilator in this group with severe COPD contrasts with the work of Chrystyn and associates who showed a small rise in FRC(He) with a fall in FRC(box) in response to treatment with slow release theophylline. Significant falls in FRC in this experiment were confined to those subjects who showed a bronchodilator response measured by change in FEV1. Trends towards a reduction were seen in the irreversible group but they failed to reach statistical significance.

TLC measured by either technique did not change following oxitropium bromide. In contrast reductions in TLC are known to occur following treatment of acute asthma (Woolcock 1971). This may be explained by the chronic adaption to hyperinflation and compensatory shortening of the respiratory muscles to maintain length tension relationships in COPD. This is known to occur in hamsters but has not been proven in man (Farkas 1983). This adaption may not occur in asthma because of the episodic and relatively short lived nature of asthmatic bronchoconstriction and hyperinflation.

The correlation between hyperinflation expressed as percent predicted FRC and airflow obstruction (percent predicted FEV1) can be explained by the relationship described by Vinegar (1979) in mice. He related FRC to  $T_e$  and the time constant of the respiratory system and showed that factors prolonging the time constants of respiratory system emptying such as airflow obstruction increased FRC above the relaxation volume of the thorax.

Resting breathlessness correlated with FRC when measured by both techniques, the relationship being stronger with plethysmographic measurements but there was a weaker relationship between end of walk breathlessness and lung volume. Reductions in breathlessness were not related to reductions in lung volumes. The stronger relationship between resting breathlessness and FRC than end of walk breathlessness may be a reflection of dynamic changes in FRC on exercise in these patients (Stubbing 1980) so that FRC measured at rest will not reflect the end expiratory position at the end of the 6 minute walk. The measurement of end expiratory position requires the use of an air conditioned plethysmograph which is beyond the scope of this laboratory. The lack of relationship between reductions in lung volume and breathlessness may reflect the variability of the measurement of lung volume and the relatively 'coarse' nature of the Borg scale. However the reductions in breathlessness in the 'irreversible patients' in the absence of lung deflation suggest that changes in FRC are not the only explanation for relief of dyspnoea although reductions in dynamic hyperinflation on exercise remain a possibility. These data suggest that while hyperinflation may be a factor contributing to the sensation of breathlessness, improvements in breathlessness following bronchodilator are not related to improvements in geometry of the

respiratory muscles and improvements in their pressure generating properties.

Chrystyn and associates postulated that the reductions in breathlessness they observed following theophylline were due to changes in trapped gas volume which itself was a sensitive indicator of small airway function. I have examined the role of trapped gas volume in the relief of breathlessness following bronchodilator.

## TRAPPED GAS VOLUME

### Introduction

Recently much interest has been aroused in the concept of trapped gas volume as a useful test of bronchodilator response, both as an indicator of those patients who will benefit functionally from bronchodilators and as a sensitive test of small airway bronchodilatation (Chrystyn 1988). However a change in trapped gas volume seems an unlikely explanation for improvements in breathlessness since it is a compound of the errors in measurement of lung volume by 2 techniques rather than an alteration in any respiratory mechanical factor.

Trapped gas volume is the difference between lung volumes measured by body plethysmography and by helium dilution. It was first described by Bedell et al (1956) shortly after his co-author Du Bois described a plethysmographic method of lung volume estimation. Comparisons were made of lung volumes measured by helium dilution and by body plethysmography in patients with lung cysts, emphysema and pneumothoraces. Trapped gas volume was the difference between FRC measured in the body plethysmograph and FRC measured by helium dilution. The difference was regarded as being solely due to underestimates of lung volume made by the helium dilution technique ie gas within the thorax which does not communicate with the mouth.

Woolcock (1971) studied lung volume changes in acute asthma by helium dilution and by body plethysmography and found that the difference between the two measures fell on recovery. The changes in FRC measured by the two methods were in the same direction, but the fall in plethysmographic FRC was much greater than fall in helium dilution FRC.

More recently Chrystyn et al reported a linear dose-related fall in trapped gas volume following treatment with theophylline in a group of COPD patients. The reduction in trapped gas volume was accompanied by dose related reductions in breathlessness scoring and improvements in 6 minute walking distance.

No data is available about the reproducibility of the measurement of trapped gas volume either within or between days, nor is any data available on the effect of other drugs on trapped gas volume. I have measured lung volumes by helium dilution and body plethysmography in a group of 32 patients with COPD on 2 successive days before and after bronchodilator. I have therefore defined the reproducibility of the measurement and have examined the effect of oxitropium bromide on trapped gas volume and its relationship to improvement in symptoms.

### Methods

Helium dilution and plethysmographic lung volumes were determined as outlined in the preceding chapters. Special care was taken to minimise artefactual errors. Trapped gas volume was defined as the difference between FRC measured by helium dilution and FRC measured by body plethysmography. This is the most 'accurate' way of defining the trapped gas volume. All other lung volume measurements are a composite of FRC -the measured volume and either an inspiratory or an expiratory manoeuvre following it and are therefore subject to greater variability.

## Results

The mean(SD) difference within and between days in trapped gas volume was small 0.16(0.64)L litres and 0.14(0.9)L litres respectively. However the 95% confidence intervals were very wide, greater than the absolute value of the measurement (within day -1.12 to 1.44L, between days -1.94 to 1.66L). The between day variability of trapped gas volume is plotted graphically in figure 7.1. The change in trapped gas volume between days and before and after medication is summarised in table 7.1. There was no relationship between trapped gas volume and either walking distance, resting or end of walk breathlessness nor to any spirometric variable.

## Discussion

These data suggest that trapped gas volume is an unsatisfactory and an unreliable measurement because of the wide 95% confidence intervals for reproducibility. This is despite the two components of the trapped gas volume measurement having reproducibilities which are as good or better than any quoted in the literature. Unlike previous authors (Chrystyn 1988) I found no relationship between changes in trapped gas volume and walking distance or breathlessness.

The reason for the differing results could be the differing definitions of trapped gas volume. Chrystyn in his work defined trapped gas volume as the difference between TLC(He) and TLC(box). Complete data of all lung volumes was obtained in 17 of the 32 patients studied. This data is summarised in table 7.2. Trapped gas volume derived from total lung capacity measurements was significantly lower than that derived from FRC measurements. The variability of the two methods of calculation were similar. There was no relationship between trapped gas volume derived from total lung capacity measurements and functional parameters. Trapped gas volume was lower when

**Figure 7.1     The between day variability**  
**of trapped gas volume**

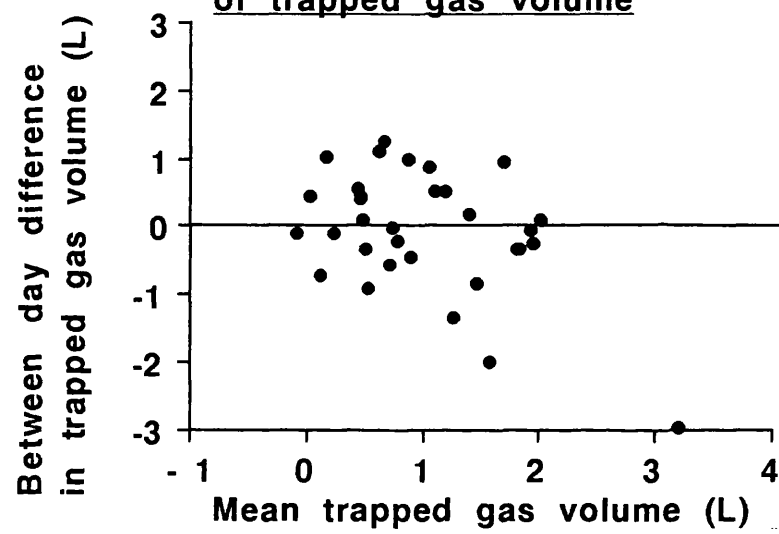




Table 7.1

Trapped gas volume determined from FRC measurements (n = 32)

| All mean(SE) | Placebo    | Oxitropium |
|--------------|------------|------------|
| Pre (L)      | 0.89(0.13) | 1.03(0.18) |
| Post (L)     | 0.91(0.14) | 0.87(0.17) |

Table 7.2

Trapped gas volume determined from TLC measurements (L)(N = 17)

| All mean(SE) | Placebo    | Oxitropium |
|--------------|------------|------------|
| Pre          | 0.26(0.24) | 0.28(0.2)  |
| Post         | 0.37(0.28) | 0.33(0.24) |

Table 7.3

Difference between inspiratory capacities between helium dilution and plethysmographic measurements (L)(N = 17)

| All mean(SE) | Placebo    |            | Oxitropium |            |
|--------------|------------|------------|------------|------------|
|              | Pre        | Post       | Pre        | Post       |
| Helium       | 1.51(0.18) | 1.33(0.18) | 1.36(0.13) | 1.72(0.17) |
| Box          | 0.85(0.09) | 0.86(0.1)  | 0.86(0.09) | 1.11(0.15) |

derived from TLC rather than FRC because of differing of inspiratory capacities measured by the two techniques. Inspiratory capacity is at least 500ml less measured in the body plethysmograph compared to helium dilution (table 7.3). Inspiratory capacity measured by either method should be the same and the difference implies that either true FRC is higher in a body plethysmograph, or that the position adopted to make a box volume measurement limits inspiratory capacity. Fixing the upper thorax is likely to alter FRC and the ability to inspire fully to TLC.

The values for trapped gas volume calculated from TLC measurements in this study are lower than those of Chrystyn et al who found values of VTG of 1.8L pre medication and 0.67L at the highest dose of slow release theophylline. The reason for the large value for TGV in the previous study may be inadequate compensation in the experimental technique for the prolonged time constants for pressure equilibration. An alternative explanation is differing sites of action of theophylline and oxitropium. However it seems unlikely that only theophylline will produce changes in trapped gas volume if such changes are real rather than artifactual.

Of the three lung volume measurements helium dilution FRC, body plethysmographic FRC and trapped gas volume, trapped gas volume was by far the most variable. For this reason it is a poor measurement and one which gives no indication to functional improvements. Whilst other measurements have their limitations and only give a limited guide to which patients will benefit from bronchodilators, their smaller variability makes them of more practical use than measurement of trapped gas volume.

## CHANGES IN AIRWAYS RESISTANCE FOLLOWING ANTICHOLINERGIC BRONCHODILATORS

### Introduction

#### The measurement of airways resistance

Before considering the effects of drugs on airways resistance, it is useful to consider the problems in the measurement of airways resistance in the plethysmograph and to review the historical background of the technique. Measurement of airways resistance was first attempted by Rohrer in 1915. He made anatomical measurements of the tracheo bronchial tree of the human post mortem lung, and calculated the cumulative airways resistance to airflow of the entire system by application of Poiseuille's law and turbulence theory. The first experimental attempt to measure pulmonary resistance in the living animal was made by von Neergard in 1927. He measured pleural pressure and obtained values for total pulmonary resistance. Several authors (Bayliss 1939, Fry 1954 and McIlroy 1955) subsequently attempted to partition total pulmonary resistance into its component elastic and resistive parts by breathing gases of differing densities, reasoning that only the resistive component would change. The results of these experiments were inconsistent. Other authors (Mead 1954, Clements 1959) measured airflow and then mouth pressure immediately after cessation of flow, reasoning that alveolar pressure immediately after mouth occlusion was the same as immediately before, and that this was accurately reflected by recordings of mouth pressure. This technique has limitations in the presence of airflow obstruction since the rate of pressure equilibration between alveolus and mouth is prolonged, and because the upper airway acts as a shunt compliance (Liistro 1989). Dubois has described 2 methods of determining airways resistance in humans, the forced oscillation technique (Dubois 1956) and the plethysmographic

method (DuBois 1955). For the plethysmographic method he reasoned that in the closed plethysmograph the total amount of gas within the box/lung system was constant. Therefore an increase in pressure of gas within the lungs must result in a decrease in the pressure of gas within the plethysmograph. If box pressure is known alveolar pressure may be calculated provided the change in box pressure for a given change in alveolar pressure is known. This is achieved by closing a shutter at the mouthpiece and making respiratory efforts against it. In the closed system behind the occlusion, mouth pressure and alveolar pressure are assumed to be equal. Thus by measuring airflow at the mouth and box pressure during respiratory movements with the shutter open and then respiratory efforts with the shutter closed, airways resistance may be calculated as the ratio of the slopes of the 2 plots.

$$R_{aw} = \frac{P_{mouth}/P_{box}}{\text{Flow}/P_{box}} \quad \text{or} \quad \frac{P_{mouth}}{\text{Flow}}$$

Because during the shutter closed manoeuvres lung volume is incidently measured then  $SR_{aw}$  may be derived.

Measurements of airways resistance are made panting. There are several practical and theoretical reasons for this

- a) to minimise 'noise' caused by box pressure drift the panting manoeuvres must be sufficiently rapid to be out of phase with environmental pressure swings.
- b)  $P_{box}$  is only a function of alveolar pressure provided no change in temperature or humidity of the respired gas occurs. For this reason the pneumotachograph is heated to 37°C, and shallow panting is employed to minimise the front of gas moving through the pneumotachograph head.
- c) Shallow panting causes the vocal cords to be abducted during measurement of airways resistance (Stanescu 1972) thus minimising the laryngeal

component of airways resistance although Higgenbottam (1982) has suggested that while the vocal cords are abducted during panting in normal individuals this may not be the case in the presence of airflow obstruction.

The potential errors of using mouth pressure to estimate alveolar pressure in the presence of airflow obstruction have been discussed previously. These errors will apply equally to the measurement of airways resistance and to the measurement of TGV, and therefore will cancel one another out in the calculation of specific airways conductance (SGaw).

### Methods

Because of problems with computer processing of some airways resistance measurements, up to a maximum of 6 separate test runs were performed until 3 satisfactory measurements of airways resistance were obtained. A satisfactory reading was defined as a manoeuvre which allowed the computer software to calculate a value of airways resistance. This was often difficult in patients with very high airways resistances and where 3 fully processed loops were not possible due to computer processing difficulty then the values from the 1 or 2 obtained were used.

### Results

Values for resting Raw were very high in all patients (table 8.1). Airways resistance and specific airways conductance were not normally distributed within the study population. Examination of the data shows this to be due to 2 patients who had extremely high airways resistances (figure 8.1). Statistical analysis has therefore been performed using only non parametric statistics, except in the calculation of correlations between resting resistance and changes in resistance following bronchodilator. The

relationships between airways resistance and spirometric variables were calculated after log transformation to normality of the airways resistance data.

The magnitude of the between day variability of airways resistance was related to the size of the measurement, as indicated in figure 8.1, but the variability of specific airways conductance was not (figure 8.2). Although the distribution of airways resistance was not normal, the relationship of the variability to the size of the measurement makes the coefficient of variation the best method of expressing variability. Accordingly the within day variability of airways resistance was 13.2% and between day 14.3%. Between day variability of SGaw was 18.4% and within day 11.5%.

#### The relationship between different measures of airflow obstruction

FEV1 and PEFr were related to each other,  $r = 0.7$ . Log Raw correlated with FEV1  $r = 0.71$  but the relationship between log Raw and PEFr was much less strong,  $r = 0.52$ . There was no correlation between changes in log Raw following bronchodilator, and the changes in either FEV1 or PEFr after bronchodilator. However the changes in FEV1 and PEFr were related to each other  $r = 0.76$ .

Oxipropium bromide caused significant falls in airways resistance in the group as a whole  $p < 0.001$  (table 8.1). The falls in airways resistance with bronchodilator were highly related to the magnitude of the measurement  $r = 0.88$ . Falls in airways resistance and increases in specific airways conductance were not confined to those who had spirometric reversibility. Significant and similar median falls in Raw being seen in both groups (tables 8.2 and 8.3), though much larger median falls in specific airways conductance were seen in those patients who had spirometric reversibility. A 26% reduction in airways resistance was seen in the irreversible group and a 34% reduction in the reversible group.

Figure 8.1

Between day variability  
of airways resistance

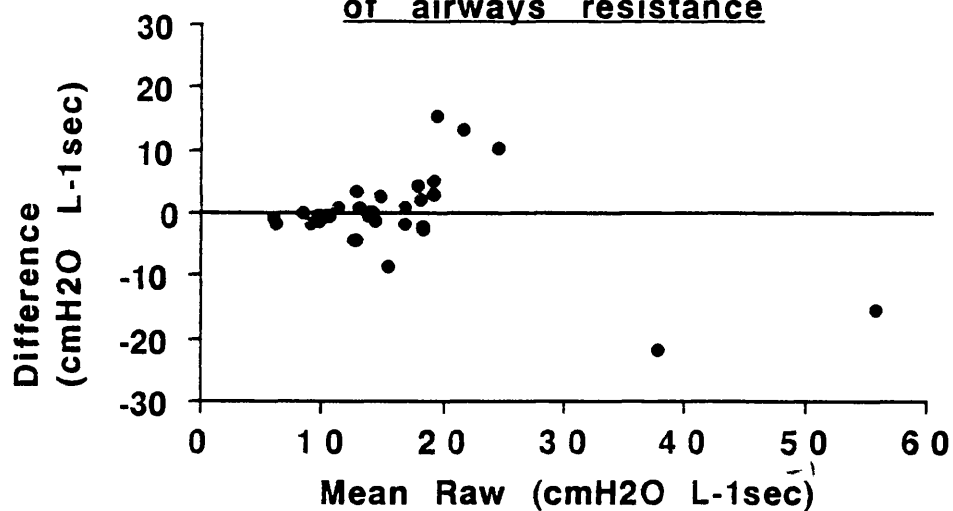


Figure 8.2

Between day variability  
of specific airways conductance

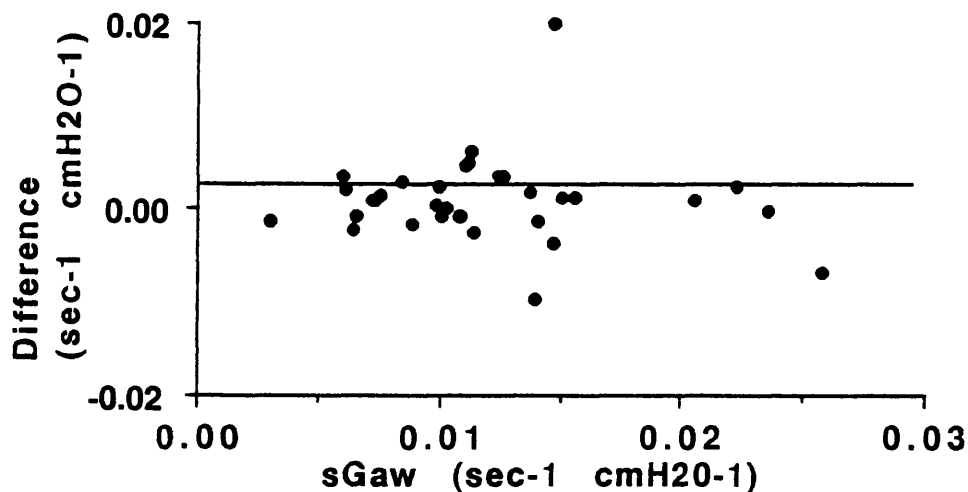


Table 8.1

Changes in airways resistance:-Whole group data

|                           | <b>Raw(cmH<sub>2</sub>O L<sup>-1</sup> s)</b><br>median(interquartile range) | <b>SGaw(s<sup>-1</sup>cmH<sub>2</sub>O<sup>-1</sup>)</b><br>median(interquartile range) |
|---------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Pre oxitropium            | 14.39 (10.44-17.6)                                                           | 0.0109 (0.0081-0.0146)                                                                  |
| Post oxitropium           | 10.97 (6.91-13.1)                                                            | 0.0152 (0.0115-0.0221)                                                                  |
| Change with<br>oxitropium | -3.98 (-6.08-1.21)                                                           | 0.0037 (0.0011-0.0078)                                                                  |
| Pre placebo               | 14.11 (10.83-19.08)                                                          | 0.01 (0.0069-0.0146)                                                                    |
| Post placebo              | 15.41 (12.46-21.18)                                                          | 0.0097 (0.0066-0.0136)                                                                  |
| Change with<br>placebo    | 0.5 (-1.00-2.72)                                                             | 0.0004 (0.0015-0.0009)                                                                  |



Table 8.2

Changes in airways resistance:-‘Reversible subgroup’ (n=12)

|                        | <b>Raw(cmH<sub>2</sub>O L<sup>-1</sup> s)</b><br>median(interquartile range) | <b>SGaw(s<sup>-1</sup>cmH<sub>2</sub>O<sup>-1</sup>)</b><br>median(interquartile range) |
|------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Pre oxitropium         | 10.61 (9.04-17.05)                                                           | 0.0134 (0.0083-0.021)                                                                   |
| Post oxitropium        | 7.09 (5.55-9.74)                                                             | 0.0246 (0.019-0.0291)                                                                   |
| Change with oxitropium | -3.65 (-5.89- -2.49)                                                         | 0.0096 (0.0057-0.0107)                                                                  |
| Pre placebo            | 10.96 (8.25-19.63)                                                           | 0.0102 (0.0067-0.0201)                                                                  |
| Post placebo           | 14.48 (8.49-19.2)                                                            | 0.00097 (0.0063-0.0097)                                                                 |
| Change with placebo    | -0.05 (-1.2-1.55)                                                            | 0.0005 (-0.0019-0.0004)                                                                 |

**Table 8.3**

**Changes in airways resistance:-‘Irreversible subgroup (n=20)**

|                           | <b>Raw(cmH<sub>2</sub>O L<sup>-1</sup> s)</b><br>median(interquartile range) | <b>SGaw(s<sup>-1</sup>cmH<sub>2</sub>O<sup>-1</sup>)</b><br>median(interquartile range) |
|---------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Pre oxitropium            | 15.67 (12.61-19.95)                                                          | 0.0103 (0.0078-0.0144)                                                                  |
| Post oxitropium           | 11.72 (10.84-16.4)                                                           | 0.0135 (0.0098-0.0173)                                                                  |
| Change with<br>oxitropium | -4.115 (-6.5- -1.12)                                                         | 0.0021 (0.001-0.0021)                                                                   |
| Pre placebo               | 15.33 (13.26-17.53)                                                          | 0.01 (0.0069-0.0143)                                                                    |
| Post placebo              | 17.15 (12.78-22.4)                                                           | 0.0095 (0.0066-0.0136)                                                                  |
| Change with<br>placebo    | 0.76 (-1.0-4.2)                                                              | -0.0004 (-0.0015-0.0015)                                                                |

**Table 8.4**

**Changes in inspiratory and expiratory resistance following placebo and oxitropium**

| All median<br>(interquartile<br>range) | Placebo                                               |                                                      | oxitropium                                            |                                                      |
|----------------------------------------|-------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------|------------------------------------------------------|
|                                        | Inspiratory<br>(cmH <sub>2</sub> O L <sup>-1</sup> s) | Expiratory<br>(cmH <sub>2</sub> O L <sup>-1</sup> s) | Inspiratory<br>(cmH <sub>2</sub> O L <sup>-1</sup> s) | Expiratory<br>(cmH <sub>2</sub> O L <sup>-1</sup> s) |
| Pre                                    | 11.60 (8.19-<br>13.07)                                | 12.29 (9.27-<br>15.97)                               | 9.67 (7.84-<br>12.95)                                 | 10.97 (8.44-<br>14.56)                               |
| Post                                   | 11.73 (9.17-<br>15.68)                                | 12.53 (8.72-<br>16.50)                               | 9.04 (6.04-<br>10.38)*                                | 9.33 (6.44-<br>10.88)*                               |

\*Significantly different from pre drug value p < 0.03

**Table 8.5**

**The effect of breathing at 1Hz on end expiratory lung volume (L)**

[All mean(SD)]

| End<br>expiratory<br>lung volume | Pre placebo | Post placebo | Pre oxitropium | Post oxitropium |
|----------------------------------|-------------|--------------|----------------|-----------------|
| Normal<br>breathing              | 6.09(1.60)  | 6.15(1.58)   | 6.06(1.44)     | 5.79(1.38)      |
| Breathing at<br>1Hz              | 7.04(1.86)  | 7.51(1.61)   | 7.04(1.86)     | 7.03(2.05)      |

Falls in expiratory resistance were larger than inspiratory resistance, though falls in both measurements were statistically significant ( $p < 0.03$ ) (table 8.4) Resting breathlessness was not related to airways resistance or sGaw, neither were falls in airways resistance significantly correlated with reductions in breathlessness or improvements in exercise tolerance.

### Discussion

Airways resistances in these patients was high, the mean Raw for the group being at least 6 fold higher than in a large series of working men (Guyatt 1968). Large and significant falls in airways resistance occurred in response to oxitropium bromide. The falls in resistance were of similar degrees in patients with and without spirometric reversibility, and in both reversible and irreversible groups exceeded the variability of the measurement. The relatively larger fall in SGaw in the spirometrically reversible group can be explained by the concurrent reductions in lung volumes in this group which were absent in the irreversible group. This suggests that changes in airways resistance are a more sensitive measure of beneficial alterations in lung mechanics in response to bronchodilators than changes in static lung volumes or spirometry.

Whilst the variability of the airways resistance measurements was high, it is in line with other series (14.3% Teculescu 1982) where an assessment of reproducibility has been made in patients with COPD, and much better than the 40 percent variability of airways resistance when measured in normal individuals (Dubois 1956). Part of the variability may be due to true variability of bronchomotor tone in these patients, and to changes in airways resistance due to differing panting volumes during different test sessions (Briscoe 1958). However the large variability of the measurement will mainly be due to the complexity of the airways resistance measurement,

requiring 2 separate complex manoeuvres. The more complex a measurement the greater its variability. Thus FEV1 has a low variability, FRC intermediate and Raw the highest.

A problem with the measurement of airways resistance in these patients with severe airflow limitation is their tendency to dynamically hyperinflate at the increased breathing frequencies required for the measurement of airways resistance. I have compared the FRC measured during normal tidal breathing with the lung volume measured after panting for the measurement of airways resistance (table 8.5). The increased breathing frequency of 1Hz used in the measurement resulted in an increase in end expiratory lung volume of between 0.5 and 1L.

Airways resistance may be a better indicator of changes in bronchomotor tone during normal tidal breathing since its measurement is performed during shallow panting when there are no large transpulmonary pressures distorting and collapsing the airways. This is important because during exercise in COPD the transpulmonary pressures do not exceed those required to produce maximal flow, whereas during the measurement of FEV1 and FVC the transpulmonary pressures are far in excess of those required to produce maximal flow. Airways resistance measurements may therefore more closely reflect improvements in ventilation during the load imposed by exercise. Airways resistance alone among the lung function tests showed significant changes in both the spirometrically reversible and irreversible groups. However the lack of correlation of measures of airways resistance with breathlessness is not surprising. While airways resistance give an indication of the load upon the respiratory system during tidal breathing, the perception of this load in terms of ventilatory depression or an increased sensation of breathlessness will vary from patient to patient. For instance individuals who are classic blue bloaters may feel less

breathless than a pink and puffing patient with a similar airways resistance. Similarly correlations between falls in airways resistance and falls in breathlessness would not be expected when resting breathlessness was not related to airways resistance and when falls in airways resistance with bronchodilator were strongly correlated with the magnitude of the measurement. The reason for this strong relationship is related to the method of calculating airways resistance. At very high airways resistance the slope of the flow/Pbox plot is very shallow and the tangent of the slope is very small. Thus relatively small changes in the slope will result in relatively large changes in the tangent. A similar explanation applies to the variability of the Raw measurements. This is the converse of the measurement of FEV1 where the 95% confidence interval of the measurement is in the order of 190mls regardless of the size of the FEV1

Expiratory resistance was slightly and significantly higher ( $p < 0.001$ ) than inspiratory resistance suggesting that although measurements were performed during shallow panting the tendency to expiratory airway collapse was not completely abolished, and suggesting that expiratory airway collapse may occur during normal tidal breathing. Further evidence of the predominant limitation to expiratory flows is provided by the shape of the tidal expiratory flow volume loop which closely resembles the maximum FV loop.

The reductions in airways resistance will have several effects on respiratory system mechanics. Lower inspiratory intrathoracic pressures will be required for a given ventilation and the need for expiratory muscle recruitment at higher ventilations will be delayed. Greater lung emptying will be permitted, and this may result in reductions in lung volumes particularly a reduction in the dynamic hyperinflation on exercise. All these findings should result in a reduced perception of breathlessness by

reducing respiratory muscle work both by lowering the work rate and by improving the efficiency of the ventilatory pump.

In summary the changes in airways resistance in response to oxitropium bromide show that bronchodilators do cause substantial beneficial changes in lung mechanics even in the absence of spirometric changes. However the improvements in breathlessness are likely to be the result of secondary changes on the respiratory muscles and effects on the dynamic changes with exercise. Nevertheless changes in airways resistance provide a large signal by which to measure the efficacy of bronchodilator medication in apparently irreversible patients.

## MOUTH OCCLUSION PRESSURE

### Introduction

In normal individuals breathlessness is closely related to levels of ventilation, which in turn are a close reflection of respiratory centre output. In patients with COPD using ventilation as a measure of respiratory centre output is confounded by the resistance of the respiratory system limiting ventilation.

Whitelaw et al (1975) proposed the use of mouth occlusion pressure as a measure of respiratory centre output. The use of this measurement followed work by Grunstein (1973) who occluded the airway of anaesthetized cats at FRC and measured the pressure developed in the trachea during the subsequent inspiratory effort. At relaxed FRC the elastic recoil pressure of the respiratory system is zero, thus the pressure measured is the net pressure generated by the respiratory muscles. Since the respiratory muscles shorten much less during an occluded breath their force velocity relationships should have minimal effect on the measured pressure. As no flow occurs during an occluded inspiration and therefore lung volume does not change (except by a small amount due to gas decompression) the measurement is uninfluenced by the flow resistance or compliance of the respiratory system. For these reasons the measurement of occlusion pressure avoids many of the mechanical factors which confound the translation of respiratory motor neurone discharge to ventilation. In cats occlusion pressure changes parallel changes in phrenic nerve activity at FRC (Evanlich 1976) and the airway occlusion pressure wave closely reflects the shape of the inspiratory neural drive (Milic-Emili 1986). For obvious reasons the tracheal pressure generated following an occluded inspiration cannot be used as a measure of respiratory centre output in



conscious man. To apply the technique to conscious human subjects Whitelaw measured the pressure generated at the mouth 100msec after the onset of inspiration ( $p_{0.1}$ ). The subjects conscious perception and reaction to the occlusion is avoided by 100msec being less than the reaction time of the subject. The measurement is made early in inspiration and therefore avoids volume related vagal reflexes. Mouth occlusion pressure as a measurement of respiratory centre output therefore depends only on neuronal discharge and the effectiveness of contraction of the respiratory muscles.

Since the generation of mouth occlusion pressure is dependent on the effectiveness of contraction of the respiratory muscles several limitations of the measurement should be considered. Changes in mouth occlusion pressure might be influenced by changes in FRC or chest wall configuration which effect resting muscle length. Eldridge (1971) found that occlusion pressure fell as FRC rose in anaesthetized cats, and Derenne (1975) reported changes in occlusion pressure with postural changes in FRC in man. In contrast Burki (1977) and Lederer (1977) found that changes in FRC of 1.4L or less on changing posture from sitting to lying did not alter occlusion pressure during either resting or CO<sub>2</sub> stimulated breathing. Grassino (1981) found no change in  $p_{0.1}$  measurements with posture during CO<sub>2</sub> rebreathing, but found that the contribution from different muscle groups varied.

Burki (1979) has related the sensation of breathlessness in COPD patients to neural drive as reflected by mouth occlusion pressure. He measured occlusion pressure at rest in breathless and non breathless patients and in a group of normal volunteers. The breathless patients had lower FEV<sub>1</sub> values but similar end expiratory lung volumes to their non breathless counterparts. Ventilation and breathing frequency were similar, but  $T_i$  was

shorter in the breathless group. Occlusion pressure was higher in the patient group than the normal volunteers, and was higher in the breathless group than the non breathless. Burki suggests that these data support the theory of length tension inappropriateness [ $p_{0.1}$  (tension) was increased relative to length (minute ventilation)]. Other authors (Rebuck 1986) have questioned the validity of  $p_{0.1}$  and  $V_e$  as measures of length and tension. Furthermore the same data could be interpreted as the increased respiratory drive being responsible for the increased perception of breathlessness if  $p_{0.1}$  is regarded as a measure of neuro muscular output when ventilation is limited by increases in impedance as in COPD.

## The effect of bronchodilators on occlusion pressure in COPD

### Introduction

Mouth occlusion pressure is a measure of respiratory centre output, and is known to relate closely to inspiratory effort sensation during resistive loaded breathing and hypercapnic stimulated breathing (Clague 1992). No data is available on the effect of bronchodilators on occlusion pressure, nor of the relationship between changes in occlusion pressure and breathlessness in response to bronchodilators.

### Methods

Mouth occlusion pressure was measured by a computerised technique during quiet unstimulated breathing in 32 patients (group biographical and lung function data is detailed earlier in this thesis and individual data is given in the appendix) before and after 200mcg oxitropium bromide administered in double blind random fashion. Subjects were seated in a constant volume body plethysmograph, and breathed on the mouthpiece assembly of the plethysmograph. Attached to the mouthpiece was a low resistance 3 way valve (PK Morgan), and attached to the inspiratory limb of this was a balloon occlusion device (Hans Rudolf model 9300). Flow at the mouth was measured using the Fleisch number 3 pneumotachograph fitted in the plethysmograph mouthpiece assembly. Mouth pressure was measured using the plethysmograph mouth pressure transducer. Outputs from mouth pressure and pneumotachograph pressure transducers were modified and connected to a dedicated microcomputer (Amstrad 1640) which measured occlusion pressure. Subjects breathed on the mouthpiece for 20-30 seconds prior to beginning occlusion measurements. Mouth occlusions were performed every 5 to 10 seconds, 5 occlusions being performed in each run. The mean of these is quoted in subsequent analysis.

Statistical analysis was by paired t tests and Spearman and Pearson correlations

### Results

Occlusion pressure measurements were obtained before and after medication in 30 patients. The between day variability of occlusion pressure measurements is shown graphically in figure 9.1. Resting occlusion pressure was elevated in these patients (table 9.1) compared to the normal volunteers studied during the validation of the computerised technique (see appendix). There was no correlation between resting occlusion pressure and resting breathlessness in these COPD patients (figure 9.2). Resting occlusion pressure correlated weakly with FEV1 ( $r = -0.36$ ;  $p < 0.05$ ), but not with other measures of airflow obstruction or with lung volume. If the 2 patients whose FEV1 was less than 0.5L and whose airways resistances measurements were very high (48 and 63cmH<sub>2</sub>O/L/sec) are excluded from the analysis resting occlusion pressure and airways resistance correlated on both days they were measured  $r = 0.42$  and  $r = 0.54$  ( $p < 0.03$  and  $< 0.002$  respectively) (figure 9.3)

Occlusion pressure fell slightly following oxitropium bromide but this fall failed to achieve statistical significance ( $p < 0.08$ ). Reductions in resting breathlessness did not correlate with falls in occlusion pressure (figure 9.4).

Subdividing the subjects arbitrarily into those who changed their FRC by >200mls following bronchodilator, and those who did not shows that those who reduced their lung volume also had significant falls in resting occlusion pressure ( $p < 0.05$ ), whereas in those whose hyperinflation was unchanged occlusion pressure fell, but the falls failed to reach statistical significance.

Figure 9.1

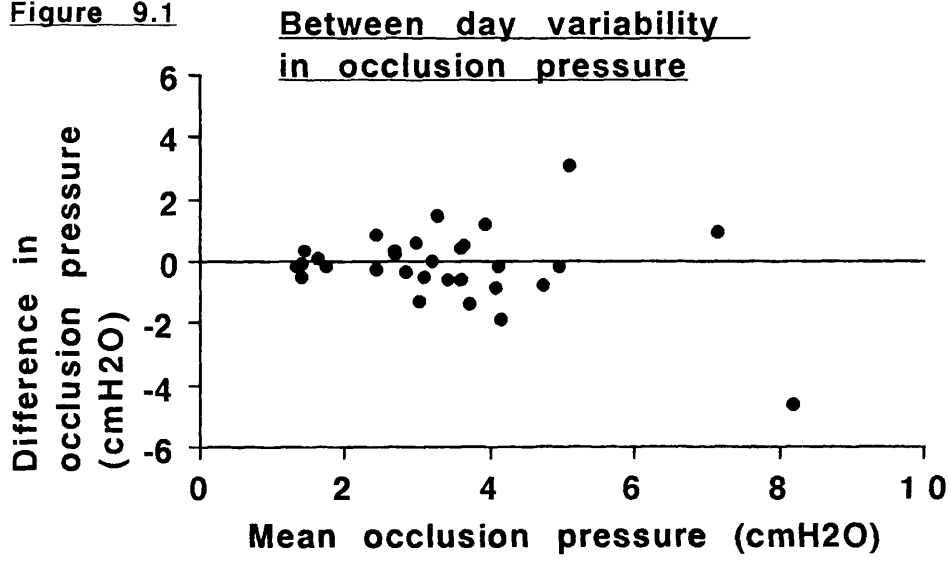


Figure 9.2

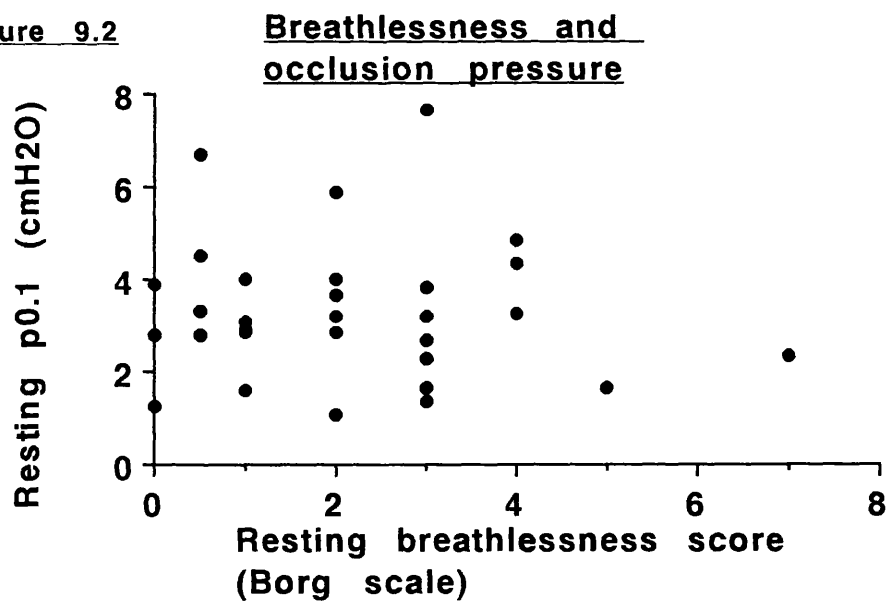


Figure 9.3

Airways resistance and  
mouth occlusion pressure

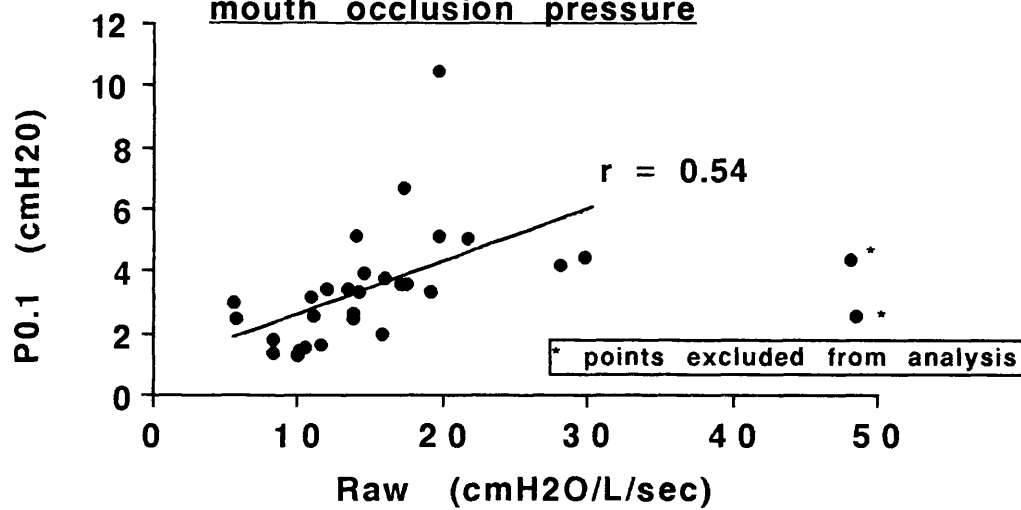


Figure 9.4

Change in breathlessness and p0.1  
following oxitropium

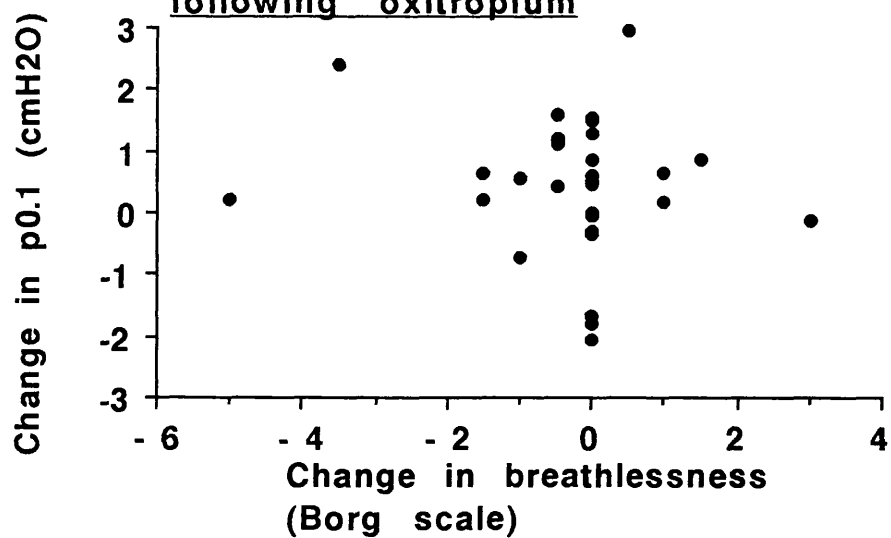


Table 9.1

Change in occlusion pressure following oxitropium and placebo (cm/H<sub>2</sub>O)

| mean(SE) | Placebo    | Oxitropium |
|----------|------------|------------|
| pre      | 3.46(0.34) | 3.32(0.27) |
| post     | 3.54(0.32) | 2.91(0.27) |
| change   | 0.07(0.22) | -0.41(0.2) |

## Discussion

The measurement of occlusion pressure in subjects with COPD may be flawed for a number of reasons. Firstly prolonged respiratory system time constants for pressure equilibration and their alteration by bronchodilator may influence the measurement (this is discussed further below) and secondly measurement of occlusion pressure assumes that relaxed FRC is reached at the end of each breath. This is often not the case in patients with severe COPD who exhibit dynamic hyperinflation and intrinsic PEEP (vide infra). These data on the effect of bronchodilators on occlusion pressure should therefore be treated with caution.

Resting unstimulated  $p_{0.1}$  was elevated in these patients with severe COPD compared to normal volunteers. However the degree of elevation of occlusion pressure is less than the values obtained in previous series (Sorli 1978). The reason for the comparatively low occlusion pressure is not clear. The computerised method gave values comparable to the manual method during the validation experiments in normal volunteers, although the measurements were not made simultaneously by both methods. A possible explanation is that the degree of airflow obstruction (assessed by FEV1) was more severe in these patients than in previous series resulting in more prolonged time constants for pressure equilibration. This will result in the incomplete pressure equilibration between alveolus and mouth at 100msec. Thus the occlusion pressure measured at the mouth will be reduced compared to the pressure developed by the respiratory muscles (which is better measured by oesophageal pressure). Experimental evidence for this hypothesis has been obtained by Murciano et al (1982) who compared occlusion pressure measured at the mouth, trachea and oesophagus in a group with severe COPD. Tracheal and oesophageal pressures were similar at iso time whereas mouth pressure



averaged only 47 percent of oesophageal pressure at iso time. A third possibility is an increased upper airway compliance in this elderly severely obstructed group of patients compared to earlier studies. This will act as a shunt compliance and reduce mouth pressure relative to oesophageal in the presence of severe airflow obstruction.

There was no relationship between occlusion pressure and breathlessness in the group as a whole. This may reflect both the variability of the unstimulated P0.1 measurements within individuals between occlusions. Five occlusions may be insufficient to compensate for this variability.

Alternatively perception of breathlessness may be influenced by factors other than the drive to breath such as mood, or personality. A closer relationship between breathlessness and occlusion pressure may have been seen within individuals under stimulated conditions such as exercise or hypercapnia when rate of change of occlusion pressure and rate of change of sensation may be compared.

Occlusion pressure was weakly related to FEV1 and more strongly to Raw (when outlying values were excluded). These variables particularly airways resistance measure the impedance to breathing, which may influence respiratory centre output, since an increased effort is required for a given ventilation. Occlusion pressure increases in response to added respiratory loads such as external resistive loads and also in response to pharmacologically induced bronchoconstriction. (Millman 1982, Kelsen 1981).

Occlusion pressure for the group as a whole was unaltered by the administration of bronchodilator, despite significant reductions in breathlessness. This somewhat surprising finding may be the result of the dependence of occlusion pressure on both the pressure generating capabilities of the thorax, and also on the pressure transmission characteristics of the airway. The administration of oxitropium bromide

resulted in both bronchodilatation and reduction in end expiratory lung volume. The former effect will result in a shortening of the time constants for pressure equilibration resulting in an enhanced transmission of pressure between alveolus and mouth thus reducing the pressure difference between these 2 sites and causing an apparent elevation of mouth occlusion pressure relative to prebronchodilator values. Reductions in end expiratory lung volume will place the diaphragm at a more advantageous part of its length tension relationship and will increase its pressure generating ability for a given motor output thus increasing occlusion pressure. Therefore modest falls in resting occlusion pressure may be masked by alterations in the physical determinants of the measurement. However the finding that significant falls in occlusion pressure occurred in the subgroup whose FRC fell by greater than 200ml suggests that reductions in neural drive to breathe (measured as  $P_{0.1}$ ) following bronchodilator are sufficiently large to overcome the mechanical changes which influence occlusion pressure measurement. Greater reductions in occlusion pressure may have been observed if oesophageal occlusion pressure measurements (which are not subject to time constant problems) had been made (A comparison between mouth and oesophageal occlusion pressure has been made in the appendix to this thesis).

It should also be noted that oxitropium bromide produced a small but significant reduction in oxygen saturation which may also have the effect of raising occlusion pressure by stimulating chemoreceptors.

## CHANGES IN OXYGEN SATURATION IN PATIENTS WITH COPD DURING 6 MINUTE CORRIDOR WALKING EXERCISE. THE EFFECTS OF BRONCHODILATOR ADMINISTRATION

### Introduction

Gas exchange inefficiency occurs in COPD (Barbera 1990), and whilst bronchodilators beneficially improve lung mechanics and expiratory airflow limitation they have the potential to worsen VQ imbalance. Alterations in blood gases may influence the sensation of breathlessness (Lane 1987) though other data suggests that hypoxia does not have an independent influence on the sensation of breathlessness (Swinburn 1984), whilst hypercapnia may also increase the sensation of breathlessness (Chonan 1990).

The effect of beta agonist bronchodilators on blood gases has been studied extensively in asthma and have been shown to cause variable falls in PaO<sub>2</sub> which are usually short lived. These small falls in PaO<sub>2</sub> are probably relatively unimportant because of the minor degrees of hypoxaemia in stable asthma, though they may be more important if similar changes occur in acute severe asthma. Several studies have addressed the effects of beta agonist bronchodilators in COPD. Stockley (1977) examined the effect of intravenous terbutaline on arterial blood gases in addition to circulatory parameters in a group of 10 subjects with cor pulmonale secondary to irreversible COPD. There was no change in PaO<sub>2</sub> following the drug, there was also no bronchodilatation measured by PEFr following intravenous terbutaline. Teule (1980) examined the haemodynamic effects of intravenous terbutaline in a group of patients with moderate to severe COPD none of whom had evidence of cor pulmonale. Terbutaline produced a small increase in PEFr and a small fall in PaO<sub>2</sub>. None of these subjects were hypoxaemic

at rest and the PaO<sub>2</sub> remained within the normal range both at rest and at exercise. Gross (1987) has compared the effects of the anticholinergic bronchodilator Atropine Methonitrate with the beta agonist bronchodilator Metaproterenol. In this study of hypoxaemic COPD patients he found that while Metaproterenol reduced resting oxygen tension Atropine Methonitrate had no effect. Hay (1990) in a study published in abstract form examined the effects of oxitropium bromide on oxygen saturation during cycle ergometry and corridor walking, and found that the degree of desaturation on exercise was slightly less following oxitropium.

In this study I have examined the effects of both the anticholinergic bronchodilator oxitropium bromide and the beta agonist bronchodilator Salbutamol on resting oxygen saturation. I have examined the extent and prevalence of desaturation during 6 minute corridor walking tests in COPD and have related resting oxygen saturation to indices of functional performance. In addition the effects of bronchodilators on oxygen saturation, breathlessness and exercise performance have been related to one another.

## Methods

### 1) The Effect of Salbutamol

23 patients with severe stable COPD (age(SD) 63.2(7)years, FEV<sub>1</sub> 0.9(0.36)L) were recruited from the outpatient clinics of Fazakerley Hospital. 22 regularly used beta agonists, 13 inhaled anticholinergics, 5 were using theophyllines and 16 inhaled steroid. Inhaled steroids were continued throughout the study period, beta agonist inhalers and anticholinergics were discontinued 6 and 12 hours respectively before each laboratory attendance whilst theophyllines were stopped 48 hours prior to attendance. After one practice 6 minute walk patients performed a baseline walk. Pulse

and oxygen saturation were recorded at the beginning, every minute during and one minute after the walk using a Biox 3700e pulse oximeter carried by a technician who followed the patient. Resting breathlessness scores were recorded prior to beginning each walk using a modified Borg scale by asking the question 'How breathless do you feel now'. 5 mg of nebulised Salbutamol or 5 ml normal saline was then administered in single blind random order. 15 minutes later a further 6 minute walk was performed with similar measurements, and finally after 2 hours a third walk was performed. No encouragement was given during the walk, but the aims of the test were stressed. Patients attended on 2 days at the same time of day 1 week apart.

## 2) The Effects of Oxitropium Bromide

35 patients with stable COPD (age(SD) 62.5(7.5)years, FEV1 0.77(0.24)L) were recruited from the outpatient clinics of Fazakerley Hospital. All had stable COPD and were irreversible (improvement in FEV1 < 200ml) to oral prednisolone (30mg daily for 2 weeks). Patients attended for 2 practice walks on separate days. Then on the third day a baseline 6 minute walk was performed. Pulse and SaO2 measurements were as above. Resting and end of walk breathlessness were recorded using a modified Borg scale. Oxitropium bromide 200 micrograms or placebo were then administered from a metered dose inhaler in double blind random order. After 1 hour's rest a further 6 minute walk was performed with similar measurements. A similar protocol with the other trial drug was followed on day 4. No encouragement was given during the walk, but the aims of the test were emphasised.

## Results

### 1) The effect of salbutamol

Resting oxygen saturation for the whole group was 91.9 (4.8)% falling significantly during the walk to a nadir of 87% ( $p < 0.001$ ). Saturation recovered quickly almost to resting levels after 1 minutes rest at the end of the walk to 90.8(5.8)%. There were no significant changes in resting, nadir or recovery saturations 15 minutes after Salbutamol administration. Two hours post drug administration the resting saturation had improved significantly to 93.6%,  $P < 0.05$ . However the nadir and recovery saturations were both unchanged (figures 10.1-10.3). The degree of desaturation during the walk was related to resting saturation ( $R = -0.45$ ) which in turn was related to FEV 1 (FEV 1 correlated with resting SaO<sub>2</sub>  $r = -0.44$ ,  $p < 0.05$ ). There was no relationship between resting saturation and the change in saturation following bronchodilator (figure 10.4). Resting saturation was unrelated to breathlessness score or walking distance, neither was the nadir saturation related to end of walk breathlessness or walking distance. Those subjects with fixed airways obstruction, ie change in FEV 1 following Salbutamol less than 200 ml, tended to have stable resting oxygen saturations in response to Salbutamol, whereas in those with significant (greater than 200 ml) bronchodilation the resting saturation tended to shift, though there was no pattern or uniformity in the direction of the shift (figure 11.5)

Figure 10.1

### Resting saturations

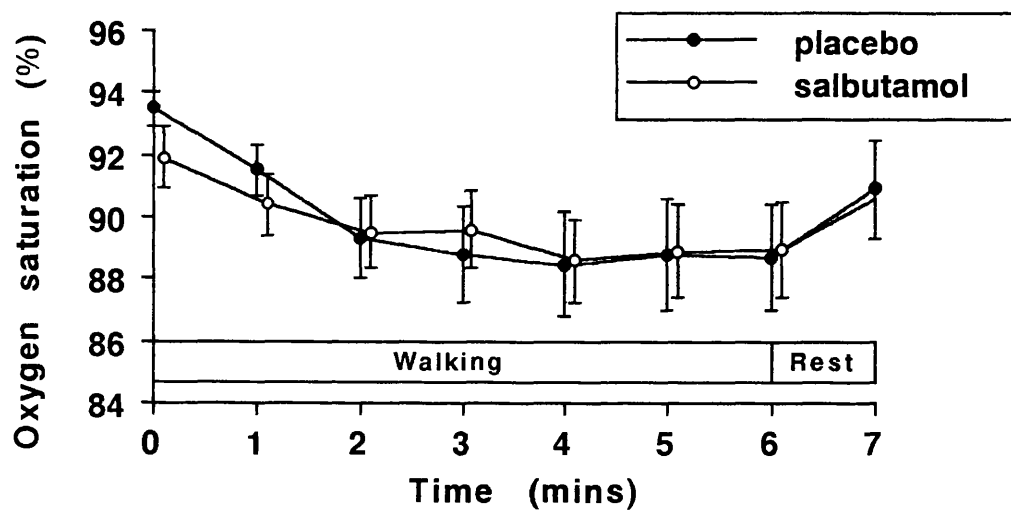


Figure 10.2

### 15 minutes post medication

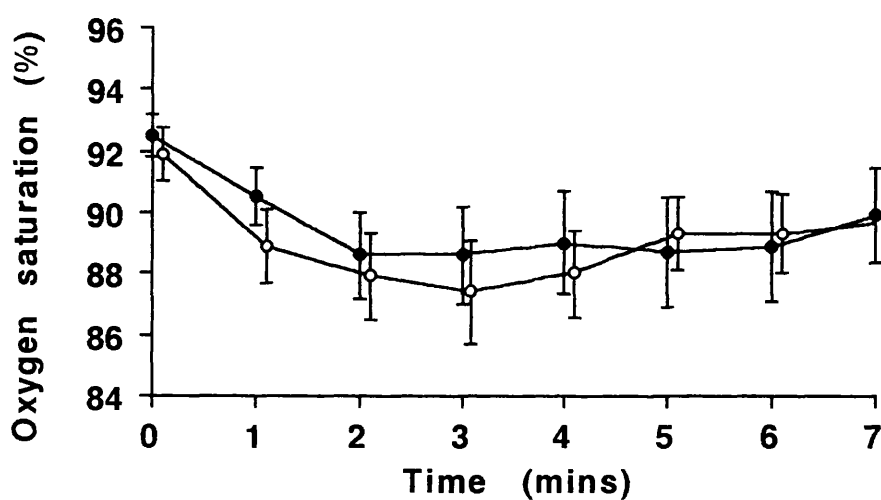


Figure 10.3

### 2 hours post medication

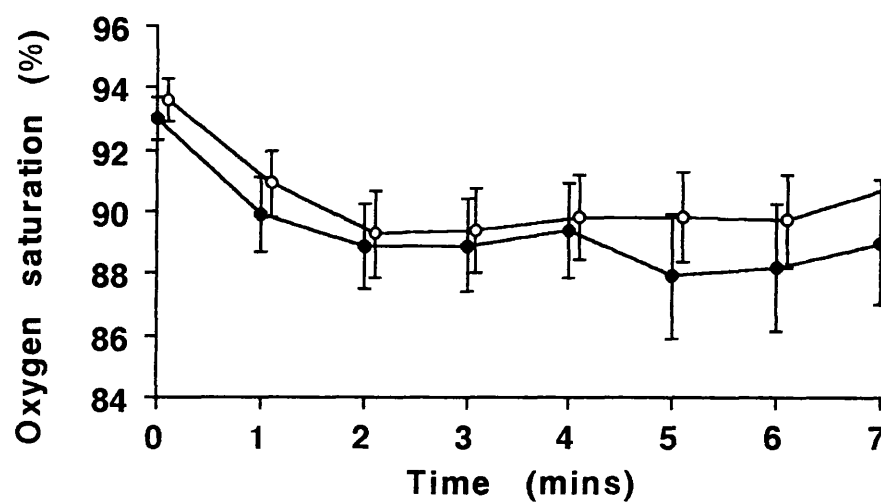


Figure 10.4 Change in resting saturation  
in response to satbutamol

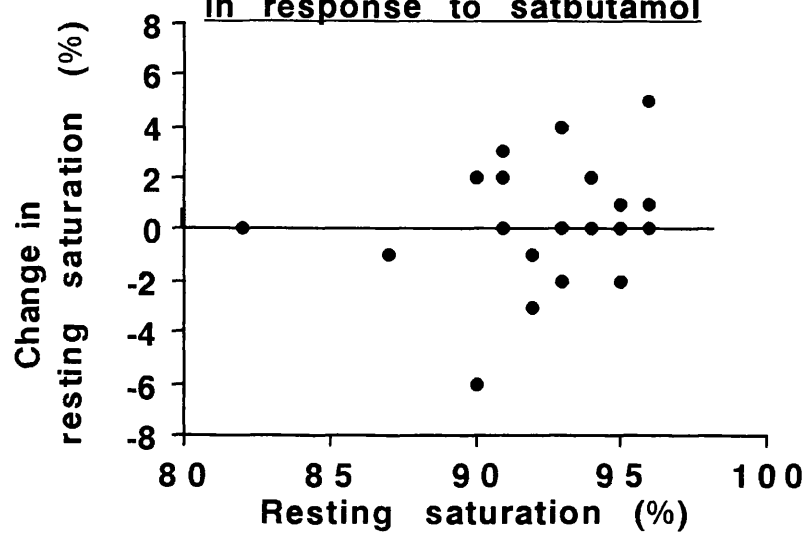
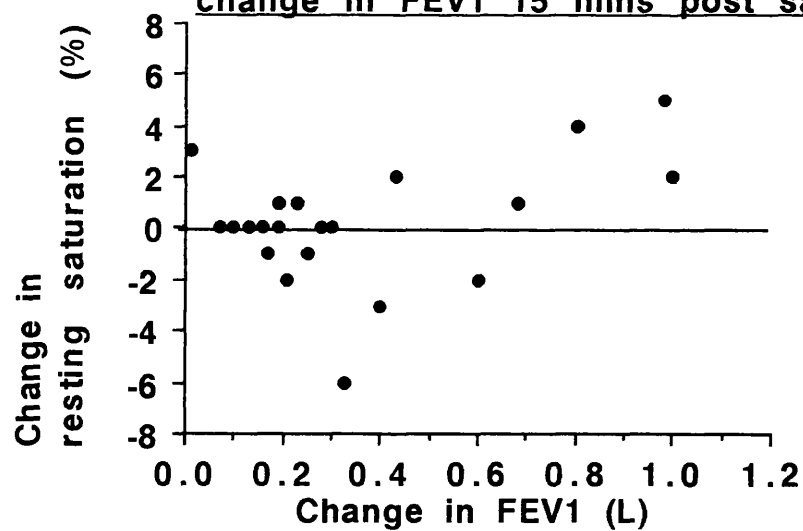


Figure 10.5 Change in resting saturation and  
change in FEV1 15 mins post salbutamol





### The effect of oxitropium bromide

8 individuals stopped during once or more during their walking tests (table 10.1). Their saturation data from during the walk is dealt with separately but their resting saturations are included in the group data. The patients who had to stop during their walks had significantly ( $p < 0.03$ ) lower resting saturations(SE) 91(1.6)% than their counterparts who did not stop 93.6(0.41)%

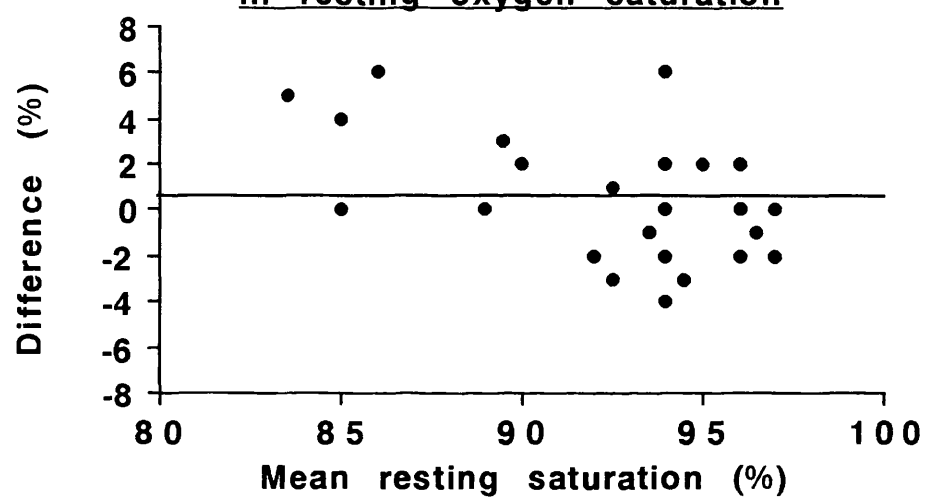
Resting oxygen saturation in this slightly more severely obstructed group was similar to that of the Salbutamol group at 92.7(0.79)%. The variability of resting saturation between days is expressed graphically in figure 10.6 Resting saturation fell slightly though significantly following 200 micrograms of inhaled oxitropium bromide to 91.7(0.83)% ( $P < 0.02$ )(figure 10.7). The nadir saturation pre-medication in this group was 88.7(1.9)% and was slightly though not significantly lower post bronchodilator. Post walk recovery oxygen saturation was 90.7(1.38)% and was slightly higher post drug 91.3(1.2)% though again this failed to reach statistical significance (figures 10.8 and 10.9). The extent of the desaturations occurring during the walk were significantly correlated with resting saturations  $r = -0.6$  ( $p < 0.001$ ) There was no correlation between resting oxygen saturation and resting breathlessness in this group but nadir oxygen saturation correlated with end of walk breathlessness  $r = -0.5$  ( $p < 0.01$ ). Resting oxygen saturation correlated with walking distance prior to medication  $r = 0.58$  ( $p < 0.001$ ). Resting and nadir oxygen saturation both correlated with baseline FEV 1  $r = 0.55$  and  $0.6$  respectively ( $p < 0.001$ ). There was no relationship between change in saturation following oxitropium bromide and resting saturation.(figure 11.9). The largest falls in resting oxygen saturation following oxitropium were in those with the smallest

Table 10.1

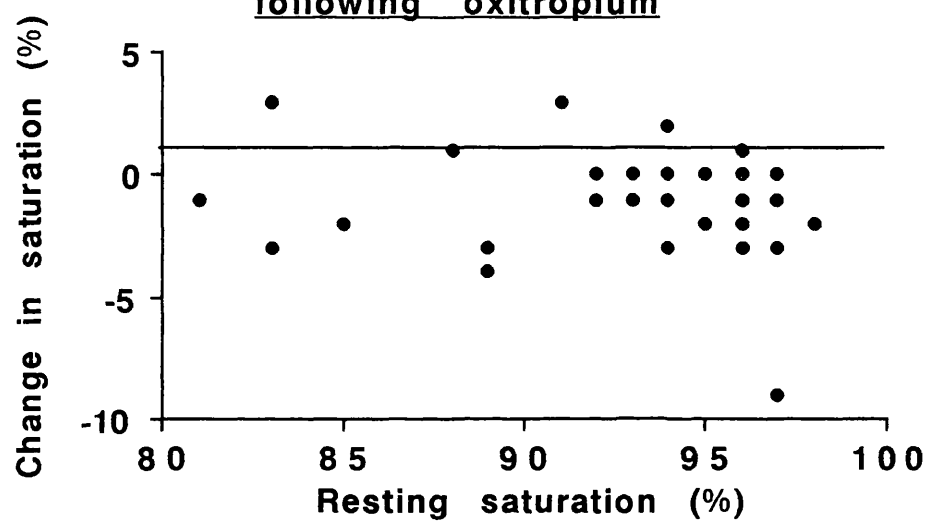
Times and saturations at stops during 6 minute walks

| Patient | Pre placebo | Post placebo | Pre Oxitropium | Post oxitropium |
|---------|-------------|--------------|----------------|-----------------|
| 6       | 4.45 84%    |              |                |                 |
| 14      |             |              | 5.55 86%       |                 |
| 21      | 1.45 81%    | 1.20 82%     | 1.30 80%       | 1.10 80%        |
|         | 2.45 79%    | 1.15 80%     | 3.00 77%       | 2.40 79%        |
|         | 4.30 82%    | 3.40 81%     |                | 4.20 79%        |
|         |             | 4.50 81%     |                |                 |
| 22      | 1.30 90%    | 1.20 84%     | 2.04 89%       | 3.30 91%        |
|         | 3.00 90%    | 4.25 85%     | 3.00 88%       |                 |
|         | 3.30 90%    |              | 5.00 87%       |                 |
|         |             |              | 6.00 88%       |                 |
| 26      |             | 4.40 87%     |                |                 |
| 27      |             | 1.45 92%     |                |                 |
| 28      |             |              | 3.45 82%       | 2.45 79%        |
| 30      |             | 3.20 71%     |                |                 |

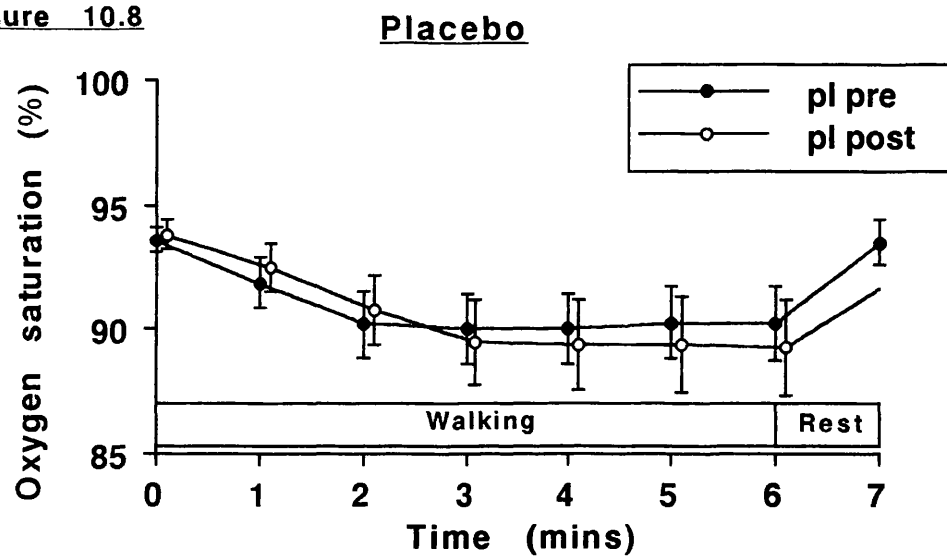
**Figure 10.6**      Between day difference  
in resting oxygen saturation



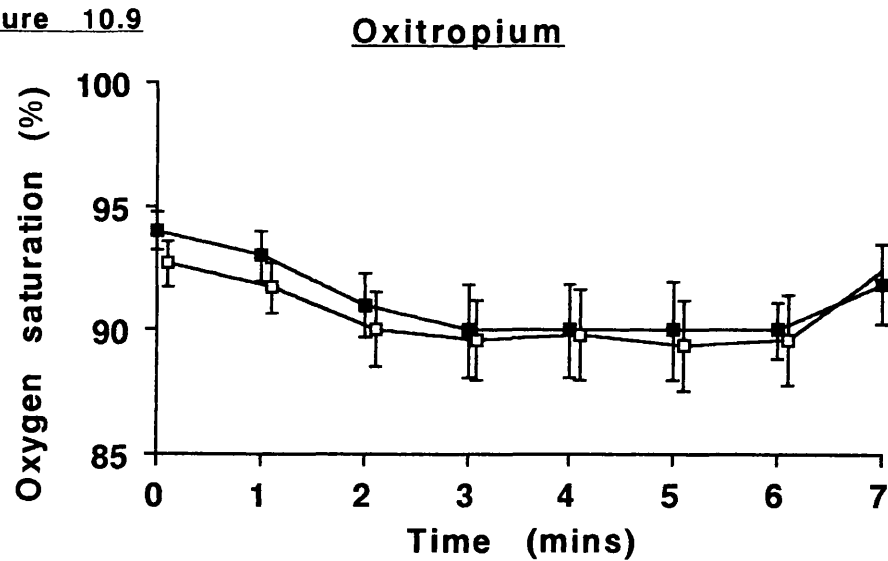
**Figure 10.7**      Change in resting saturation  
following oxitropium



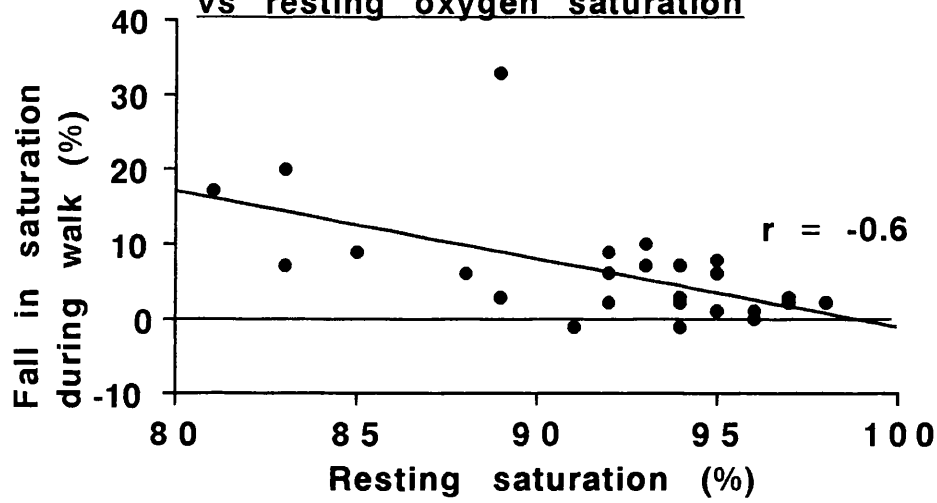
**Figure 10.8**



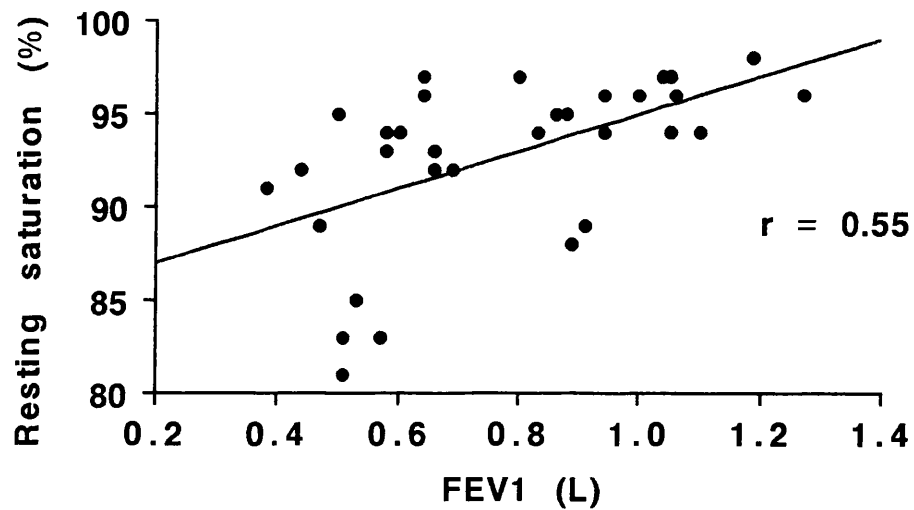
**Figure 10.9**



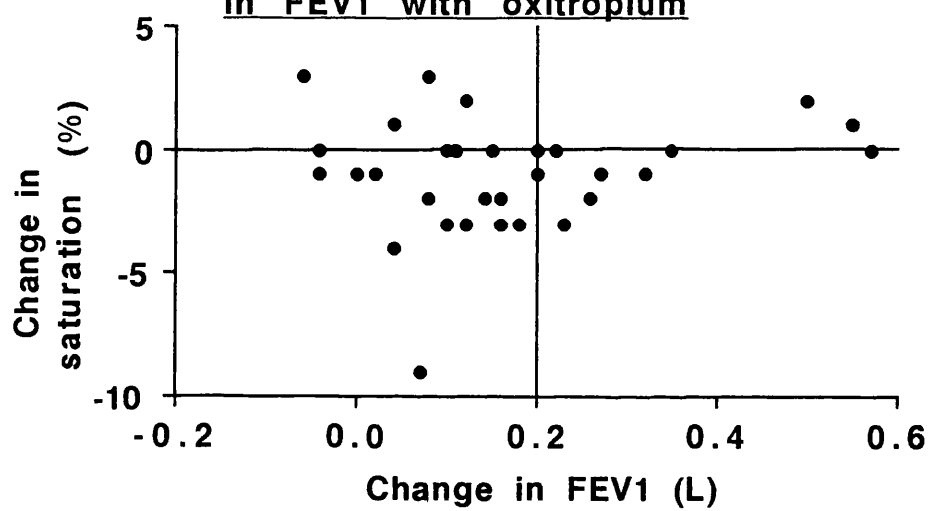
**Figure 10.10** Fall in oxygen saturation during walk  
vs resting oxygen saturation



**Figure 10.11** Resting saturation and FEV1



**Figure 10.12** Change in saturation and change in FEV1 with oxitropium



bronchodilator response ( $R = 0.46$ ), however these irreversible patients also had the lowest baseline FEV<sub>1</sub> and therefore the lowest resting oxygen saturations.

#### The thirteen subjects who performed both experiments

I was able to compare the effects of both bronchodilators in a small sub group of patients who performed both experiments. Oxitropium caused a significant reduction in the resting oxygen saturation in this small group as in the main group, there being a fall in SaO<sub>2</sub> compared to placebo of 2.1% (3.04)  $P < 0.02$ . Salbutamol showed no effect on resting saturations. Neither drug had any effect on the nadir oxygen saturation during exercise.

#### Discussion

These experiments have confirmed that corridor exercise causes oxygen desaturation in patients with severe COPD. The degree of desaturation during walking exercise is similar to that published by Hay et al (1990) who also noted that desaturation was less during cycle ergometry. The brisk early fall in saturation during the walk followed by a steady state may be due to the initial burst of speed at the beginning of the 6 minute corridor walk, followed thereafter by a relatively constant walking speed (Morice 1984, Butland 1982).

Unlike previous studies I have examined the effect of different classes of drugs on desaturations during 6 minute walking tests. As expected those with the lowest resting oxygen saturations desaturated the most during exercise. This can be explained simply by the shape of the oxygen haemoglobin dissociation curve, where those lying on the steepest part of the curve desaturate the most for a given fall in PaO<sub>2</sub>. I did not show a change in resting oxygen saturation 15 minutes after Salbutamol, this is in



contrast to the work of Gross and Bankwala (1984) who showed that Metaproterenol caused a significant fall in PaO<sub>2</sub> of 5 mm Hg in a group of patients with hypoxic COPD. These authors also examined the effect of the nebulised anticholinergic atropine methonitrate on resting oxygen saturation in the same group of hypoxemic patients; again their results contrast with ours as they did not show any fall in arterial oxygenation with this drug. The data of Hay et al (1990) who found no significant effect of oxitropium bromide on saturation in a small group with COPD and similar degrees of airflow limitation also contrast with these findings. Even when the sub group who are the most hypoxemic are studied in isolation (those patients whose resting saturation was less than 92%) there was no change in the resting oxygen saturation following Salbutamol. Other authors (Peacock 1983 and Teule 1980) have shown similar effects on arterial oxygenation to Gross et al with various beta agonist bronchodilators (Isoprenaline, Pirbuterol and Terbutaline). The work of Stockley et al is (1977) in agreement with our study, they showed no changes in arterial oxygen tension following intravenous terbutaline. The reason for the difference between the studies is not clear as all contained patients with similar degrees of airflow limitation. Possible explanations include differing modes of drug administration or different degrees of bronchodilator and cardiovascular action of each beta agonist. Oxitropium caused more desaturation than Salbutamol in the same patients; a possible explanation is Salbutamol having more cardiovascular effects than oxitropium with either improvements in cardiac output, or more close matching of blood flow and ventilation following salbutamol. The improvement in resting oxygen saturation observed 2 hours post Salbutamol administration (even though bronchodilator effect was slightly reduced) suggests that any VQ imbalance following salbutamol is short

lived, and raises the possibility that bronchodilators administered regularly may improve oxygen saturation. No data is available on the duration of desaturation caused by oxitropium bromide.

The degree of variability of baseline oxygen saturation may partially be explained by the method of measurement, the pulse oximeter depends on highly amplified and filtered signals to provide saturation data and is therefore probably only reliable within 2% within an individual. Similarly small changes in saturations derived from group data should be treated with a degree of caution.

The lack of relationship between resting oxygen saturation and resting breathlessness suggests that arterial oxygen saturation is not an important determinant of breathlessness. Likewise nadir oxygen saturation only correlated weakly with end of walk breathlessness in one of the two studies suggesting that oxygen desaturation is not an important determinant of exercise breathlessness in this group of patients. This data is in agreement with the work by Swinburn et al (1984) who showed that the relationship between ventilation and breathlessness during exercise in COPD is not altered by prevention of hypoxaemia suggesting mechanical factors are more important than humoral ones. Conflicting results have been published by Lane et al (1987) who found that preventing desaturations during treadmill exercise reduced breathlessness, a fall which could not be explained by reductions in exercise ventilation consequent upon oxygen administration.

All desaturations recorded at rest following bronchodilator were small and unlikely to be of any acute clinical significance, although it is conceivable that regular administration of anticholinergic bronchodilators may add slightly to the overall hypoxic burden of patients with severe COPD.

## THE EFFECT OF PHARMACOLOGICALLY INDUCED BRONCHOCONSTRICTION ON BREATHLESSNESS IN COPD

### Bronchial reactivity in COPD

Bronchial reactivity occurs in 3% of the normal population and in most patients with asthma. It is also seen in a large proportion of patients with COPD. Yan et al (1985) in a community based study found 27/59 patients with COPD had bronchial reactivity (group geometric mean PC20 in COPD patients 1.62micromols/l) though there was considerable overlap in reactivity between asthma and COPD. In addition bronchial reactivity was related to starting airway calibre in COPD but not in asthma.

Yan has suggested that the bronchial reactivity of asthma and COPD are different, pointing out that though there is marked overlap between PC20 values, the slope and position of the dose response curve are clearly different when group data are examined. Taylor et al (1985) have shown that bronchial reactivity to histamine is greater in smokers than non smokers, and that increased bronchial reactivity is associated with an accelerated decline in FEV1. However the smokers also had a lower FEV1, and therefore might have been expected to have increased bronchial reactivity. There was no increase in bronchial reactivity in young smokers whose FEV1 was normal. There was no relationship in vitro between PC20, cholinergic bronchoconstriction and adrenergic smooth muscle relaxation in COPD. The authors concluded that in COPD enhanced bronchial reactivity is not related to an increased smooth muscle response to contractile agents, nor to deficiencies in the adrenergic inhibitory mechanisms.

Several authors (Chung 1984, Yan 1985 and Ramsdale 1984) have found that bronchial reactivity in COPD is strongly influenced by starting airway calibre suggesting that the increased reactivity is geometrically determined. Other authors (DuToit 1986) have suggested that central

deposition of aerosol droplets may be responsible for increased reactivity. There is some experimental evidence to support this view as Agnew (1981) has shown that central airway deposition is predominant when FEV1 falls below 60% predicted

Bronchodilator drugs are known to influence bronchial reactivity in both COPD and asthma (Higgins 1991, Bel 1991). Bel et al have shown that salbutamol reduces bronchial reactivity and increases the slope of the dose response curve in both asthma and COPD. Anticholinergic bronchodilators have only limited effect on bronchial reactivity, and no data is available on the effect of anticholinergic agents on the slope of the dose response curve. In particular there is only limited data on the effect of oxitropium bromide on bronchial reactivity.

Pharmacologically induced bronchoconstriction increases breathlessness and occlusion pressure in normal individuals and in patients with asthma and COPD (Oliven 1985, Kelsen 1981) but the relationship between the complex load imposed by bronchoconstriction and breathlessness is not well characterised. In the experiment described in this chapter changes in lung mechanics have been induced with histamine and these changes have been related to changes in breathlessness and occlusion pressure. This model produces 'contrasting' changes in lung mechanics compared to those brought about by bronchodilators and therefore facilitates further study of mechanisms of breathlessness in COPD. In addition the effect of anticholinergic bronchodilatation on bronchial reactivity has been examined.

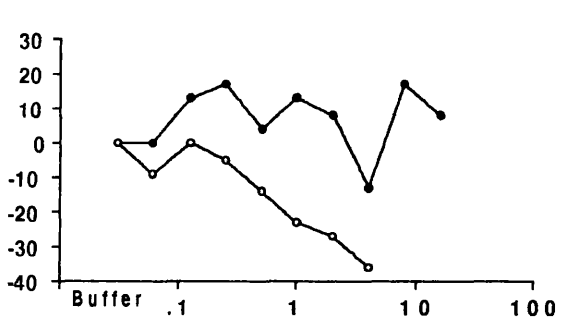
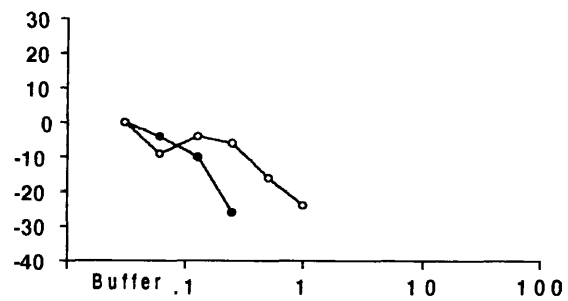
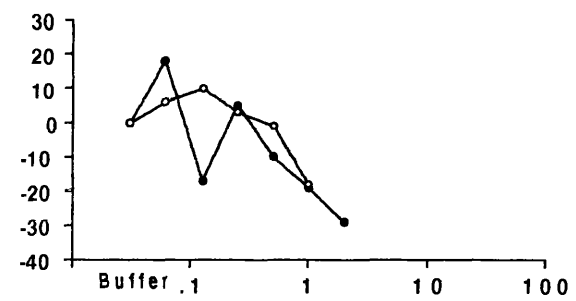
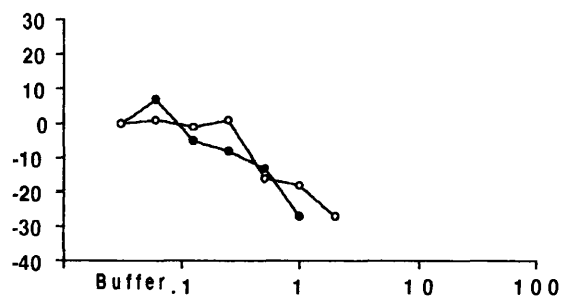
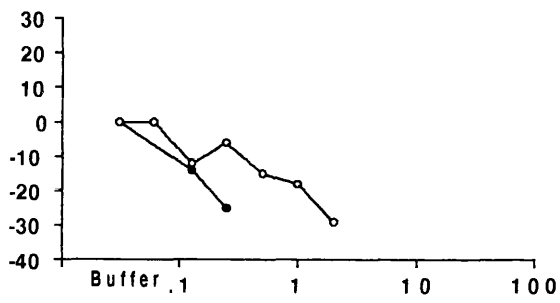
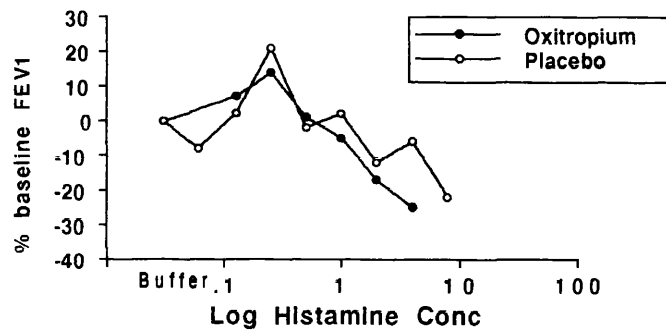
## Methods

14 patients with COPD were recruited from outpatient clinics at Fazakerley Hospital (Table 11.1). All gave informed consent and the study was approved by the local ethical committee. All patients were irreversible to oral steroid (30mg prednisolone for 2 weeks) and had an FEV1 greater than 0.8L. All abstained from oral bronchodilators for at least 24 hours, anticholinergic inhalers for at least 12 hours and beta agonists for 6 hours prior to attending the laboratory on both test days. Either 200 mcg oxitropium bromide or placebo from a MDI was administered in double blind random fashion and after 1 hour histamine challenge was performed by the dosimeter method (Chai 1975) using a custom built dosimeter. The nebulisation time of the dosimeter was 2 seconds beginning 0.5 seconds following the onset of an inspiration. Patients inhaled slowly 5 times from RV to TLC holding their breath at TLC after each inhalation. FEV1 (best of 2 measurements within 5%) was measured 1 minute after each dose of histamine. Histamine was administered in doubling concentrations until a 20 percent fall in FEV1 was provoked. Lung volumes were measured in a constant volume body plethysmograph (panting at 1Hz) before the challenge and after a 20 percent fall in FEV1. Occlusion pressure was measured by a computerised technique detailed earlier in this thesis and breathlessness was assessed at the beginning and end of the challenge using a modified Borg category scale by asking the question "How breathless do you feel now".

## Results

### The effect of oxitropium bromide on bronchial reactivity

These patients with severe steroid irreversible COPD exhibited non specific bronchial hyperreactivity to histamine, group geometric mean PC20 0.96mg/ml. Oxitropium produced significant bronchodilation in this group of patients (table 11.1) but had no effect on either bronchial reactivity, or the slope of the dose response curve (figures 11.1-11.14). There was no relationship between bronchial reactivity and bronchodilator reversibility to either oxitropium bromide or salbutamol (figures 11.15 and 11.16), or between the change in bronchial reactivity with oxitropium and increase in FEV1 with the bronchodilator. There was no relationship between bronchial reactivity and the degree of airflow obstruction expressed as percent predicted FEV1 in this group of patients (figure 11.17).



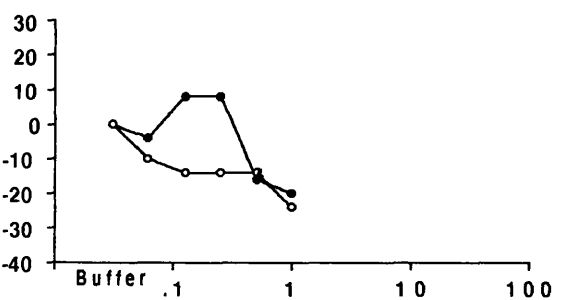
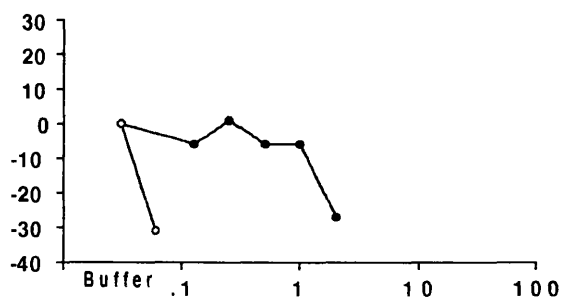
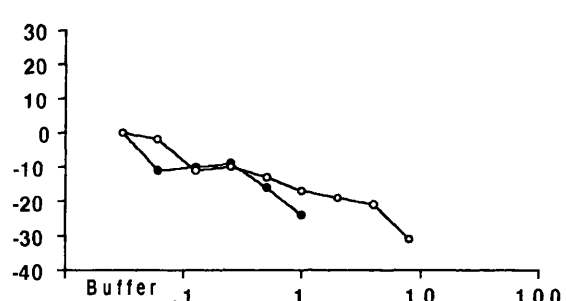
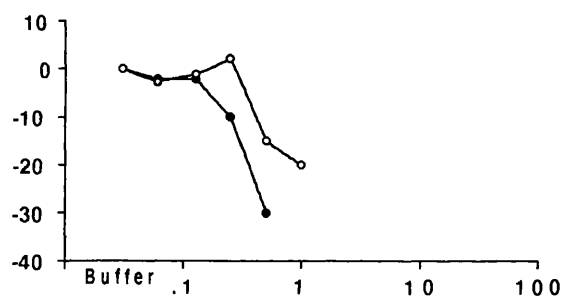
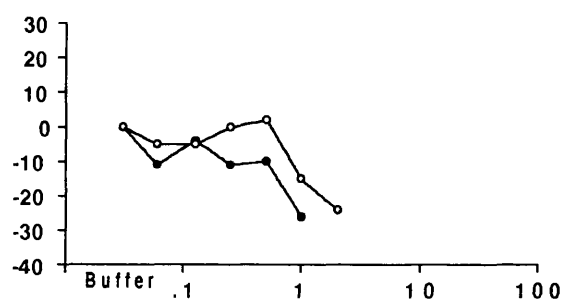
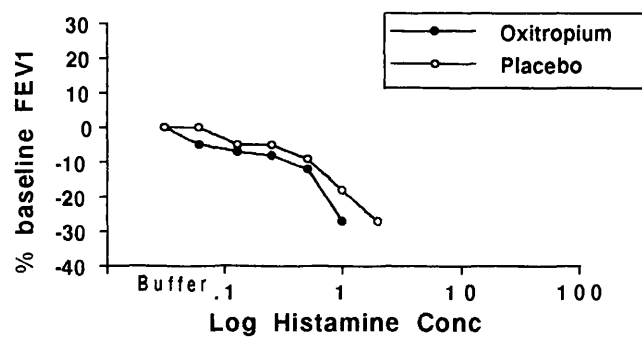




Table 11.1

The effect of oxitropium on bronchial reactivity

| FEV1 (L) | %pred FEV1 | oxitropium<br>reversibility<br>(L) | salbutamol<br>reversibility<br>(L) | PC20<br>Placebo<br>(mg/ml) | PC20<br>oxitropium<br>(mg/ml) |
|----------|------------|------------------------------------|------------------------------------|----------------------------|-------------------------------|
| 1.01     | .31        | .2                                 | .25                                | 8                          | 2                             |
| 1.34     | .34        | .35                                | .33                                | 2                          | .7                            |
| 1.08     | .38        | .32                                | .45                                | .85                        | .25                           |
| .94      | .27        | .08                                | .35                                | .5                         | 1                             |
| 1.3      | .46        | .55                                | .15                                | 1.4                        | .15                           |
| 1.11     | .35        | .27                                | .03                                | .5                         | 4                             |
| 1.1      | .35        | .23                                | .1                                 | 2                          | 1                             |
| 1.1      | .34        | .16                                | .58                                | 1                          | 1 6                           |
| .87      | .38        | .12                                | .49                                | 1                          | .2                            |
| .94      | .26        | .57                                | .55                                | .06                        | 1.6                           |
| .84      | .24        | .12                                | .25                                | 6                          | .75                           |
| .95      | .49        | .1                                 | .05                                | 4                          | 2                             |
| 1        | .40        | .22                                | .59                                | 1.9                        | .75                           |
| 1.05     | .28        | .26                                | .2                                 | 1                          | 1                             |

**Table 11.2**

The effect of oxitropium and histamine on lung function (n = 10)

| all mean (SE)                  | Pre<br>challenge (Pl) | Post<br>challenge (Pl) | Pre<br>challenge (Ox) | Post<br>challenge (Ox) |
|--------------------------------|-----------------------|------------------------|-----------------------|------------------------|
| FEV1 (L)                       | 1.07(0.05)            | 0.76(0.04)             | 1.25(0.09)            | 0.99(0.08)             |
| FRC (L)                        | 5.96(0.49)            | 6.44(0.61)             | 5.66(0.49)            | 5.88(0.59)             |
| TLC (L)                        | 6.73(0.46)            | 7.08(0.58)             | 6.58(0.47)            | 6.65(0.52)             |
| Breathlessness<br>(Borg scale) | 2.15(0.38)            | 4.2(0.66)              | 1.85(0.44)            | 3.5(0.66)              |
| P0.1 (cm/H <sub>2</sub> O)     | 3.1(0.57)             | 4.5(0.92)              | 3.1(0.35)             | 3.72(0.46)             |

Figure 11.15

Histamine reactivity  
and oxitropium reversibility

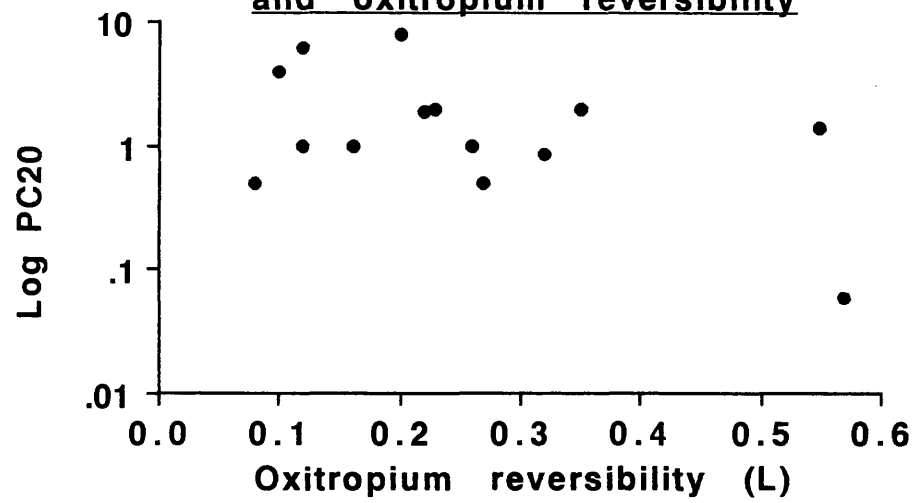
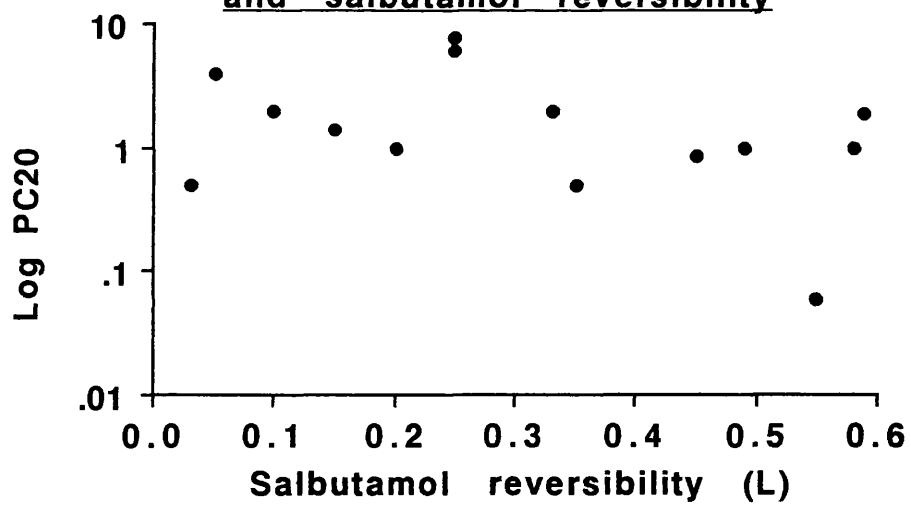
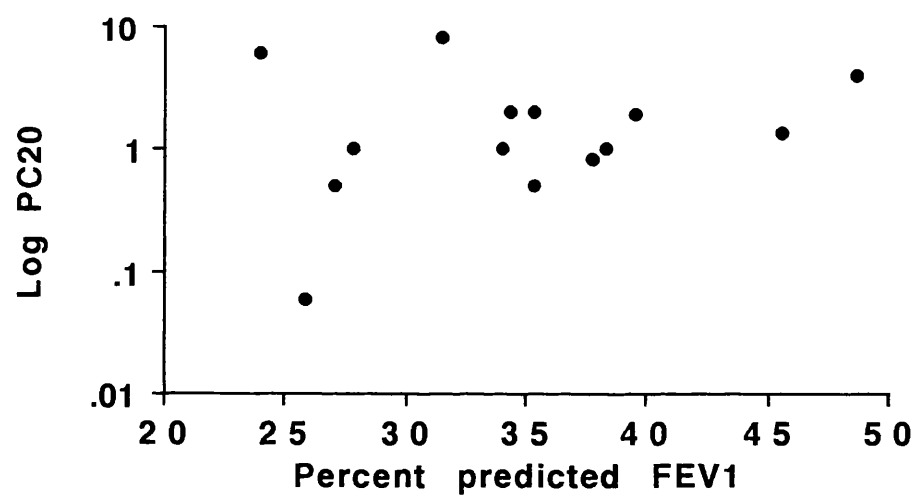


Figure 11.16

Histamine reactivity  
and salbutamol reversibility



**Figure 11.17**      Histamine reactivity  
and airflow obstruction

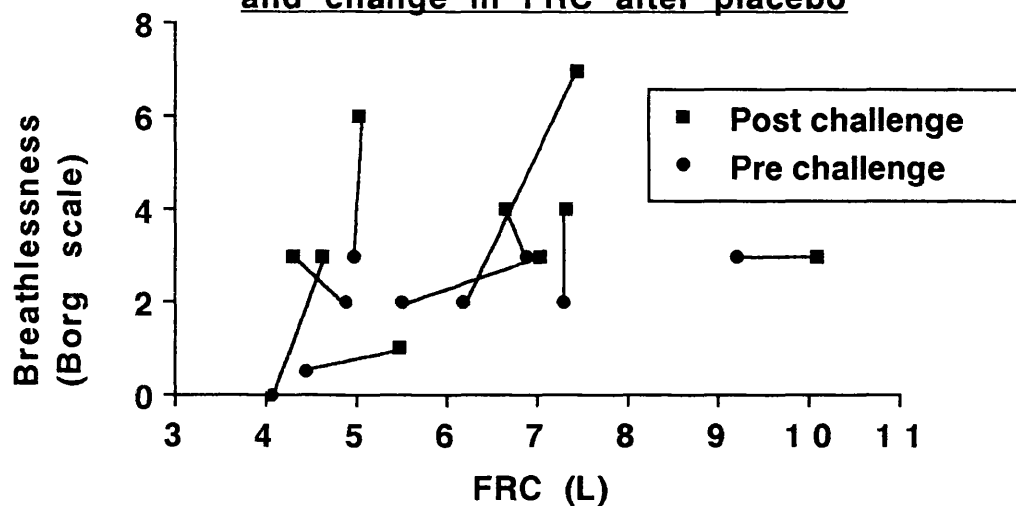


The effect of histamine induced bronchoconstriction on lung volume, breathlessness and occlusion pressure.

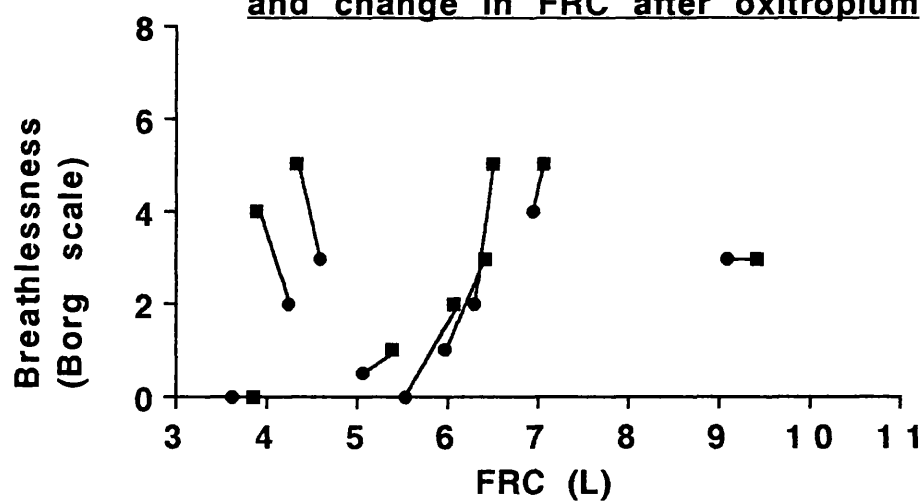
In 10 patients lung volumes were measured before and at the end of the histamine challenge on both test days. In the remaining 4 individuals increased breathlessness induced by the histamine challenge made lung volume measurement intolerable. Changes in spirometry and lung volume have been related to changes in breathlessness and occlusion pressure.

Histamine challenge caused FRC to rise on both days (table 11.2, figures 11.18 and 11.19), but only on the placebo day did the rise achieve statistical significance ( $p < 0.05$ ). Pre challenge FRC fell in this small group following bronchodilator administration, but the fall failed to reach statistical significance ( $p < 0.08$ ). The FRC measured at the end of the challenge, after PD 20 had been reached was significantly reduced following oxitropium bromide ( $p < 0.001$ ). Breathlessness and occlusion pressure both increased significantly during the challenge on both test days ( $p < 0.001$ ). Resting breathlessness and occlusion pressure were not significantly reduced by the administration of oxitropium bromide, end of challenge breathlessness was unchanged, and the reduction in end of challenge occlusion pressure also failed to achieve statistical significance. TLC was unchanged either by the histamine challenge or by bronchodilator administration.

**Figure 11.18** Change in breathlessness  
and change in FRC after placebo



**Figure 11.19** Change in breathlessness  
and change in FRC after oxitropium



## Discussion

These patients with steroid non responsive COPD exhibit a similar degree of bronchial hyperreactivity as has been observed in previous studies of bronchial reactivity in COPD where the selection criteria have been less rigorous (Britton 1988, Higgins 1991, Bel 1991). Steroid non responsiveness is perhaps the best way of excluding those with late onset asthma, although a subgroup of asthmatics do eventually become steroid non responders. The reason for the observed bronchial hyperreactivity in COPD may be geometric due to bronchial narrowing, unlike the bronchial hyperreactivity seen in asthma which may be due to either an increased contractility of bronchial smooth muscle in response to histamine or methacholine, and/or due to bronchial wall thickening. However if bronchial hyperreactivity were purely geometric in COPD then the bronchodilatation induced by oxitropium bromide (which is a relatively "pure" anticholinergic agent with little effect on smooth muscle contractility) might be expected to reduce it since the bronchodilator increases airway calibre (as measured by increases in FEV1 and falls in Raw). It is possible that the falls in lung volume which accompany the bronchodilatation may increase bronchial reactivity. Data from Ding et al (1987) showed that the bronchial reactivity of normal volunteers was influenced by end expiratory position, reductions in FRC of 0.5L resulting in increases in bronchial reactivity, whereas increases in FRC of a similar magnitude reduced the non specific bronchoconstrictor response. Spence et al (1992) in a study recently published in abstract form using a different model have confirmed the increased bronchial reactivity at reduced lung volumes in normal subjects but found no effect of reduced lung volume on bronchial reactivity in asthmatic individuals. Whether bronchial reactivity in COPD is influenced by airway parenchymal interdependence is not known, but if reductions in lung volume do enhance

reactivity then the effect of bronchodilatation on bronchial reactivity may be negated.

Anticholinergic bronchodilators might also be expected to reduce bronchial reactivity in a pharmacological manner. This may have been more likely had the bronchoconstricting agent used been methacholine which has a direct effect on bronchial smooth muscle and whose action would have been more likely to be inhibited by oxitropium bromide.

The small effect of anticholinergic bronchodilators upon bronchial reactivity has been demonstrated before both in asthma and in COPD with a variety of agents (atropine sulphate, atropine methonitrate and ipratropium bromide) (Tattersfield 1987, Britton 1988). Higgins (1991) in a recently published study found that bronchial reactivity was reduced by ipratropium bromide by 0.56 doubling doses in group of less severely obstructed patients than those in this study. These small changes in bronchial reactivity following anticholinergic bronchodilator drugs are in contrast to the large reductions in bronchial reactivity which have been demonstrated with B agonist agents. Higgins reported a fall in bronchial reactivity with salbutamol in the same group of patients of 1.9 doubling doses, and Bel et al (1991) reported an even greater fall, a five fold reduction in bronchial reactivity being recorded following salbutamol administration in a group with mild to moderate COPD (percent predicted FEV1 61.6%). This group also found the slope of the dose response curve to histamine and methacholine was increased following salbutamol administration in both COPD and asthma. I found no effect on the slope of the dose response curve with oxitropium bromide. The relevance of the slope of the dose response curve is unclear. Bel et al postulate that an increase in the slope of the dose response curve suggests an increased predisposition to catastrophic bronchoconstriction but this is unproven.



The reason for the differing effects of salbutamol and anticholinergic medication on bronchial reactivity and asthma may be a direct effect on the contractility of smooth muscle induced by salbutamol.(Davis 1982)

The lack of correlation between PC20 or change in PC20 and bronchodilator reversibility is in agreement with the work of Higgins and Bel. However the lack of relationship between reactivity and initial airway calibre contrasts with several previous studies (Chung 1984 and Yan 1985), possibly because in these patients with severe airflow obstruction effort dependent airway collapse makes FEV1 a relatively poor guide to airway dimensions during relaxed tidal breathing. However in spite of this there was a wide range of bronchial reactivity in this relatively homogeneous group of COPD patients. The severe airflow obstruction in these patients meant it was impossible to determine a plateau in the dose response curve. Work by Bel et al suggests that a plateau is reached in only a minority of patients with COPD.

The rise in occlusion pressure seen during histamine challenge has been observed before in COPD, and is in keeping with increased sensation of breathlessness experienced towards the end of the histamine challenge. Oliven et al (1985) using data obtained during histamine challenge in patients with less severe COPD than in this study has suggested that the rise in occlusion pressure is solely related to hypercapnia during the challenge, and have suggested that when the rise in CO<sub>2</sub> is allowed for then no change in occlusion pressure is observed. However no allowance was made for the rises in FRC which occur during a challenge which may result in a reduced pressure generating ability of the respiratory muscles and therefore a reduced occlusion pressure as discussed in previous chapters of this thesis. I did not measure end tidal CO<sub>2</sub> or ventilation during these challenges and am therefore unable to comment on the effect of CO<sub>2</sub> on our

results. Data from normal individuals and from patients with asthma (Millman 1982 and Kelsen 1981) have suggested that occlusion pressure does rise during induced bronchoconstriction, and interestingly Millman found that the occlusion pressure response was abolished by airway anaesthesia with lidocaine.

The rise in FRC which I have shown is similar to that which occurs in asthmatic patients during induced bronchoconstriction. It may be either a compensatory mechanism to maintain expiratory flows in the presence of an increased resistance, or an attempt to minimise airway narrowing by histamine by breathing at higher lung volume to minimise airway closure. Alternatively the rise may be a passive phenomenon resulting from an increased lung emptying time. Evidence from asthmatics suggests that rises in FRC are dynamically determined, and the presence of intrinsic peep in patients with COPD would also suggest that hyperinflation is dynamically determined.

The relationship between breathlessness and altered lung mechanics during histamine challenge is complex, and several factors are interrelated. The increased resistance to airflow brought about by bronchoconstriction results in an increased work of breathing since higher intrathoracic pressures are required to produce a given airflow. This in turn requires an increased neural activation of the respiratory muscles which results in an increased "effort" of breathing a sensation which is closely related to the sensation of breathlessness. The rise in end expiratory lung volume which occurred during the challenge may reduce diaphragmatic efficiency and further increase respiratory muscle work predisposing to respiratory muscle fatigue. This situation may also occur during acute exacerbations of COPD when respiratory muscle fatigue is known to result in respiratory failure. However end of challenge breathlessness was unchanged following oxitropium

despite falls in the end of challenge FRC of 600ml suggesting that changes in FRC alone are not central in the genesis of dyspnoea resulting from induced bronchoconstriction (figures 11.18 and 11.19). This may also have implications in interpreting the changes in breathlessness occurring during exercise when dynamic hyperinflation may influence breathlessness, and agrees with the finding that reductions in breathlessness occurring following bronchodilator occurred in the absence of changes in end expiratory lung volume.

In addition to these mechanical factors bronchoconstriction may stimulate airway mechanoreceptors. Kelsen et al (1981) showed that the level of dyspnoea in normal individuals was greater with induced bronchoconstriction than when with external loading to produce the same resistance. Taguchi (1989) in a study published in abstract form reported that airway anaesthesia reduced dyspnoea secondary to histamine induced bronchoconstriction but had no effect on the breathlessness induced by external loading. However it should be recognised that the sensation of dyspnoea induced by external loading may be distinct from that induced by bronchoconstriction (Simon 1989,1990).

Lastly the effort of performing a histamine challenge in such severely obstructed patients may induce fatigue and breathlessness. This could be assessed by incorporating a sham challenge in future studies.

In summary, pharmacologically induced bronchoconstriction increases breathlessness, but the relationship between this increase and mechanical factors is not a simple one, with many interrelated factors playing a role.

## The effect of oxitropium bromide on breathlessness during progressive isocapnic hypoxia and progressive hypercapnia.

### Introduction

The study of the effects of bronchodilators on ventilation during corridor exercise is difficult because the subject is mobile. Alternatively ventilation during exercise may be studied by cycle ergometry but this form of exercise is unfamiliar to patients with severe COPD. For this reason reflex stimulated breathing by both progressive hypercapnia and isocapnic hypoxia offers an attractive model in which to study the effect of bronchodilatation on breathlessness in relation to alterations in respiratory system mechanical dynamics. In addition the model allows the study of the ventilatory responses to different chemical stimuli and also the perceptual changes in response to increases in ventilation. It also has the advantage that the subject is stationary and is using only the respiratory and accessory muscles. This allows the accurate measurement of gastric and oesophageal pressures free from movement artefact.

Studies of the respiratory responses to hypercapnia and hypoxia are extensive and have assessed the respiratory response in terms of ventilation, occlusion pressure and sensation. Adams 1985 and McCloskey 1978 studied ventilation, finding that the ventilatory response to hypercapnia and hypoxia was reduced in COPD. This finding is usually attributed to the increased mechanical load on the respiratory system in COPD. The use of the occlusion pressure response (Altose 1976, Kelsen 1979, Gribben 1983, Gorini 1989) overcomes some of the problems of the increased mechanical impedance to breathing which may confound using ventilation as a measure of respiratory centre output but assumptions upon which occlusion

pressure measurement are based may not be valid. The sensory response to hypercapnia and hypoxia have also been studied (Stark 1981, Chonan 1990, Lane 1987) by measuring perceived breathlessness using psychophysical techniques.

While the effects of external resistive loads and of induced bronchoconstriction on breathing pattern and perception of breathlessness during reflex stimulated breathing have been studied (Altose 1977, Kelsen 1979, Clague 1992), the effect of unloading breathing by bronchodilators has not.

The sensation of breathlessness is closely related to levels of ventilation although there is some evidence to suggest that dyspnoea may be heightened by hypercapnia (Chonan 1990) and by hypoxemia (Lane 1987). I have studied the effect of bronchodilators on breathlessness induced by both the above stimuli and have related changes in breathlessness to changes in ventilation and other respiratory variables.

## Methods

6 patients with severe COPD were studied. All were irreversible to oral steroid (30 mg prednisolone daily for 2 weeks). All had abstained from inhaled beta agonists for at least 6 hours and inhaled anticholinergics for at least 12 hours prior to the study. None used oral bronchodilators and all other medication was continued unchanged. All patients gave informed consent and the study was approved by the local ethical committee.

Oesophageal and gastric balloon catheter systems were inserted transnasally following nasal and pharyngeal anaesthesia with 4% lignocaine. Both balloons were inserted into the stomach (determined by a positive pressure swing on sniffing), then 1 balloon was withdrawn until a negative pressure swing on sniffing was evident. The balloon was then withdrawn a further 5cm so that its entire length was in the oesophagus. Both balloons were then emptied of air and 0.5ml of air was inserted into both. Cardiac and tracheal artefact were checked for and the balloons were secured in position. Mouth, oesophageal and gastric pressures were measured using Gould P23XL pressure transducers.

Lung volumes were measured in a constant volume body plethysmograph panting at 1Hz, the value quoted being the mean of 3 measurements. Flow volume loops were performed on a rolling seal spirometer, the value quoted being the best of three measurements.

The patient was seated in front of the rebreathing circuit which was adjusted for maximal comfort (figure 12.1) . Flow was measured using a Fleisch No 2 pneumotachograph and volume derived by electronic integration of the flow signal. Flow, volume, mouth, gastric and oesophageal pressures were recorded simultaneously onto a Gould 6 channel chart recorder. A 30 second period of resting breathing was recorded with the subject breathing on the pneumotachograph disconnected from the circuit. This data was used

to calculate resting PEEPi dyn and assess breathing pattern before and after bronchodilator. A CO<sub>2</sub> rebreath was then performed. Respiratory sensation was measured every 30 seconds using a modified Borg scale the subject being asked the question "How much effort does it take to breathe". Mouth occlusion pressure was measured every 3-6 breaths at random throughout the rebreath by the manual method detailed in the appendix to this thesis. End tidal CO<sub>2</sub> was recorded every 10 seconds (Engstrom Eliza CO<sub>2</sub> analyser) and oxygen saturation every 10 seconds by ear oximetry (Biox 3700e). Rebreathing was continued until terminated by the patients symptoms, or when the end tidal CO<sub>2</sub> reached 9.9% (the limit of the analyser range). When the patient had recovered from this after 10 minutes an isocapnic hypoxemic rebreathing experiment was performed making similar recordings. This test was terminated when the oxygen saturation fell to 75%. Dynamic intrinsic PEEP was calculated according to the method described by Haluszka et al (1990)(figure 12.2) and may be defined as the residual elastic recoil of the respiratory system at the end of an expiration immediately prior to the onset of the following inspiration.

## Results

### Changes in resting breathing

The results of the resting unstimulated breathing experiment are summarised in tables 12.1 and 12.2. Four of the six subjects studied increased their FEV1 by  $\geq 200\text{ml}$  following oxitropium bromide whilst in the remaining 2 subjects the increase was  $100\text{ml}$ . FRC fell in 5 out of 6 subjects ( $p < 0.01$ ), the largest falls being in those individuals who had the largest degree of bronchodilatation measured spirometrically. Resting minute ventilation increased in all subjects from (SE)  $14.4(1.6)\text{L}$  to  $17.0(2.1)\text{L}$  ( $p < 0.01$ ) following the bronchodilator. There was no pattern to the changes in duty cycle following oxitropium. Inspiratory time lengthened in 4, shortened in 1 and was unchanged in 1, while Ttot lengthened in 4 and shortened in 2 subjects. Four of the 6 subjects scored their resting breathlessness lower following the drug and in 2 it was unchanged. The reduction in breathlessness was unrelated to the changes in either FEV1 or FRC.

PEEP1 dyn was present in 5 of the 6 cases and fell where present from (SE)  $5.43(1.5)\text{cmH}_2\text{O}$  to  $2.2(0.8)\text{cmH}_2\text{O}$  following oxitropium ( $p < 0.02$ ). The fall in PEEPi was not related to changes in FEV1 or FRC.

Inspiratory pleural pressure swings were less during resting breathing following bronchodilator in 3 of the 6 patients and was unchanged in the other 3.



Figure 12.1

A patient performing a stimulated breathing experiment

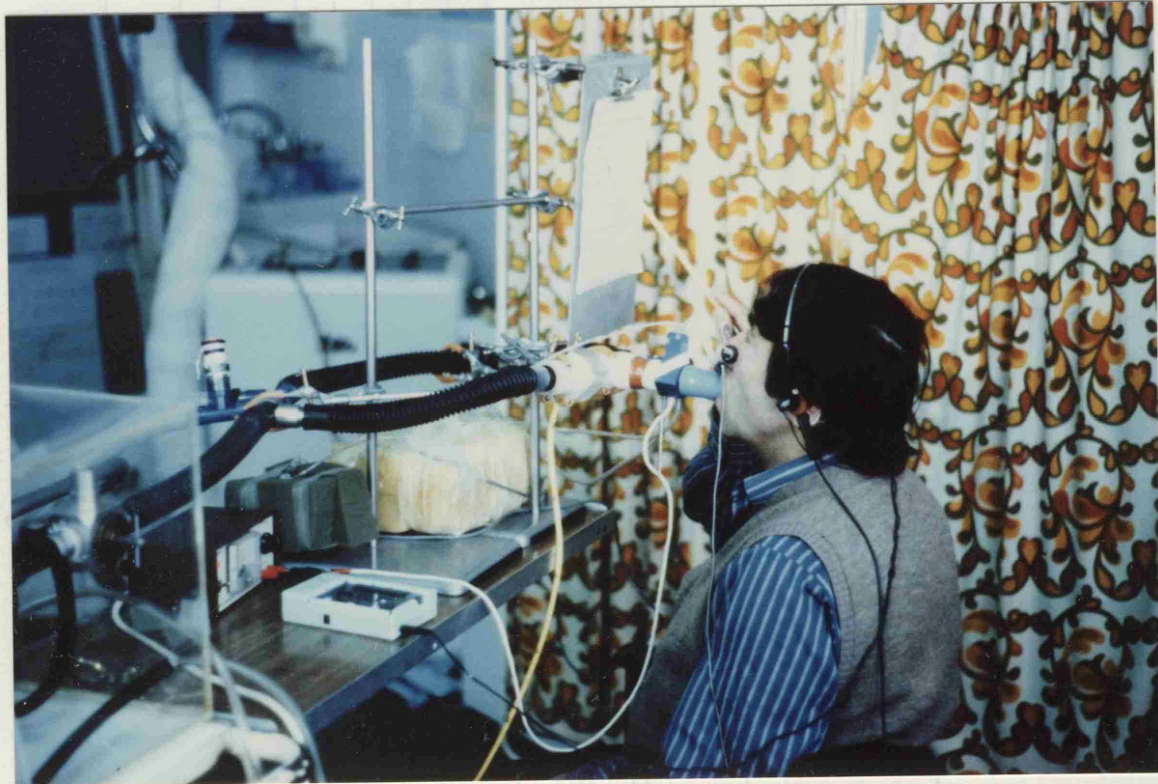


Figure 12.2

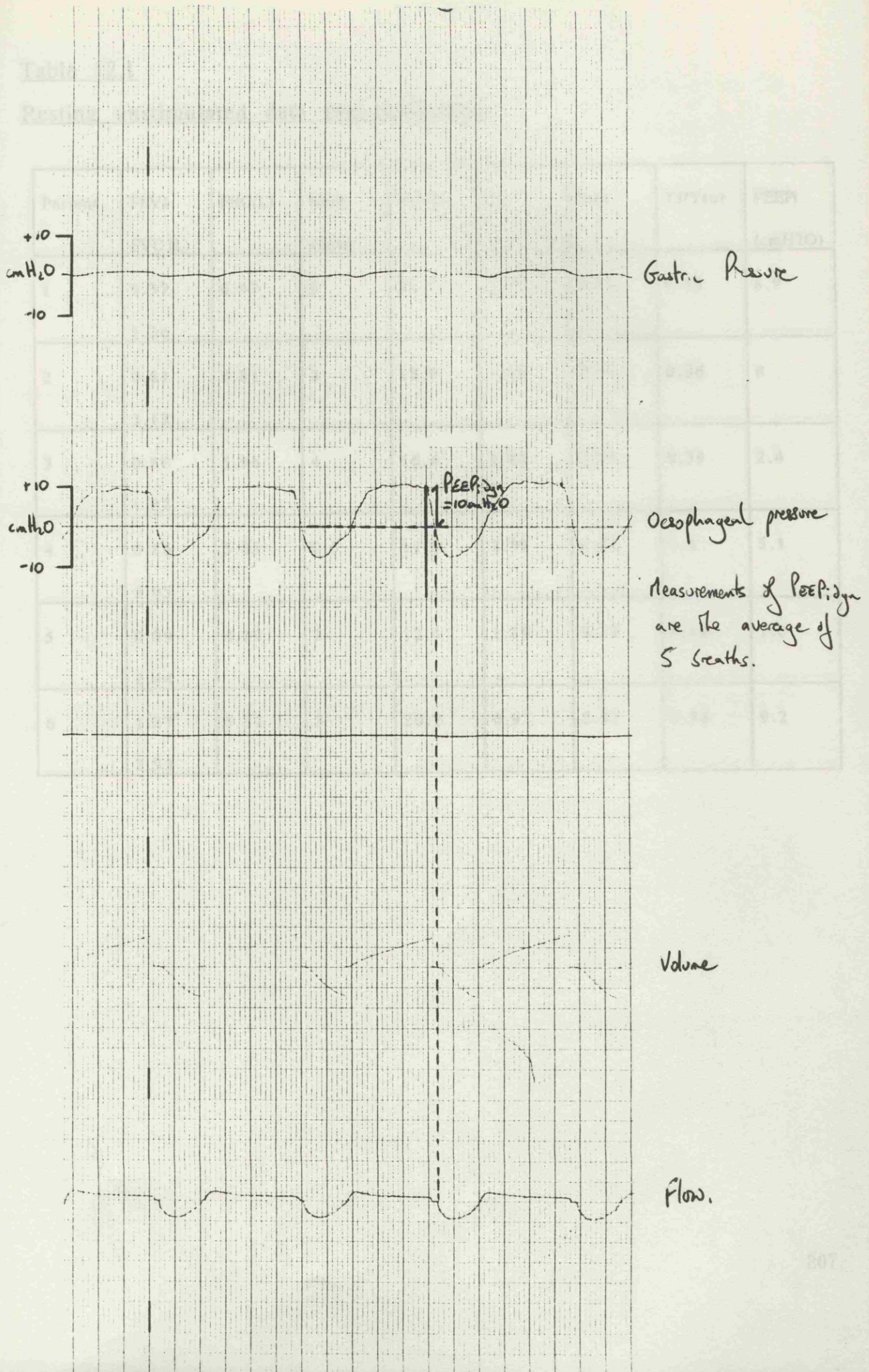


Table 12.1

Resting unstimulated data pre medication

| Patient | FEV1<br>FVC (L) | FRC(L) | Borg<br>score | Ve (L) | Ti   | Ttot | Ti/Ttot | PEEPi<br>(cmH2O) |
|---------|-----------------|--------|---------------|--------|------|------|---------|------------------|
| 1       | 0.37<br>1.36    | 6.47   | 3             | 10.5   | 0.97 | 2.98 | 0.33    | 8.9              |
| 2       | 0.81<br>3.12    | 8.81   | 3             | 15.9   | 1.06 | 2.94 | 0.36    | 0                |
| 3       | 0.86<br>1.82    | 5.96   | 4             | 16.4   | 1.06 | 2.74 | 0.39    | 2.4              |
| 4       | 0.86<br>2.05    | 5.65   | 0.5           | 11.0   | 2.39 | 5.91 | 0.4     | 5.1              |
| 5       | 0.89<br>2.44    | 4.29   | 2             | 12.4   | 1.79 | 4.29 | 0.42    | 7.0              |
| 6       | 1.27<br>2.33    | 5.82   | 3             | 20.2   | 0.9  | 2.52 | 0.36    | 9.2              |



Table 12.2

Resting unstimulated data post medication

| Patient | FEV1<br>FVC (L) | FRC (L) | Borg<br>score | Ve (L) | Ti   | Ttot | Ti/Ttot | PEEPi<br>(cmH2O) |
|---------|-----------------|---------|---------------|--------|------|------|---------|------------------|
| 1       | 0.47<br>1.54    | 6.53    | 0.5           | 12     | 0.89 | 3.49 | 0.26    | 5.5              |
| 2       | 1.01<br>4.22    | 7.78    | 3             | 18.6   | 1.16 | 2.49 | 0.47    | 0                |
| 3       | 0.94<br>1.94    | 5.03    | 3             | 19.05  | 1.11 | 2.56 | 0.43    | 0.9              |
| 4       | 1.15<br>2.76    | 4.79    | 0.5           | 12.4   | 2.26 | 6.0  | 0.38    | 1.3              |
| 5       | 1.32<br>2.98    | 3.48    | 0             | 14.1   | 1.88 | 4.33 | 0.43    | 1.8              |
| 6       | 1.62<br>2.88    | 4.33    | 2             | 25.6   | 1.07 | 2.77 | 0.39    | 3.9              |

### Changes in ventilation during stimulated breathing

Ventilation, PEEPi and inspiratory pleural pressure all increased during the course of both the hypoxic and hypercapnic breathing runs (tables 12.3 and 12.4) The relationship between these variables and perceived breathlessness was inconsistent. Mean inspiratory flows were increased post bronchodilator in all patients at the end of the hypercapnic experiments compared to the pre bronchodilator values ( $p < 0.01$ ) and in 4 individuals during resting breathing (table 12.5). Inspiratory pleural pressure was reduced at equivalent levels of ventilation following oxitropium bromide, implying increased efficiency of ventilation (figure 12.3).

The onset of expiratory abdominal activity during the hypercapnic experiments was delayed following bronchodilator in all cases where present, and was reduced in magnitude at peak ventilation (tables 12.6 and 12.7).

Although starting breathlessness was reduced by oxitropium bromide, the slope of the IES/ $V_e$  relationship was unaffected by the administration of bronchodilator. Neither was there any difference between the slopes of the IES/ $V_e$  relationship between hypoxic and hypercapnic runs (Table 12.8).

There was no consistent change in the in the slopes of the  $O_2$ /IES or  $CO_2$ /IES responses (Table 12.9), or in the slopes of the  $V_e/CO_2$  and  $V_e/O_2$  responses following bronchodilator. (Table 12.10)

**Figure 12.3**     Inspiratory pleural pressure  
and ventilation in 1 individual

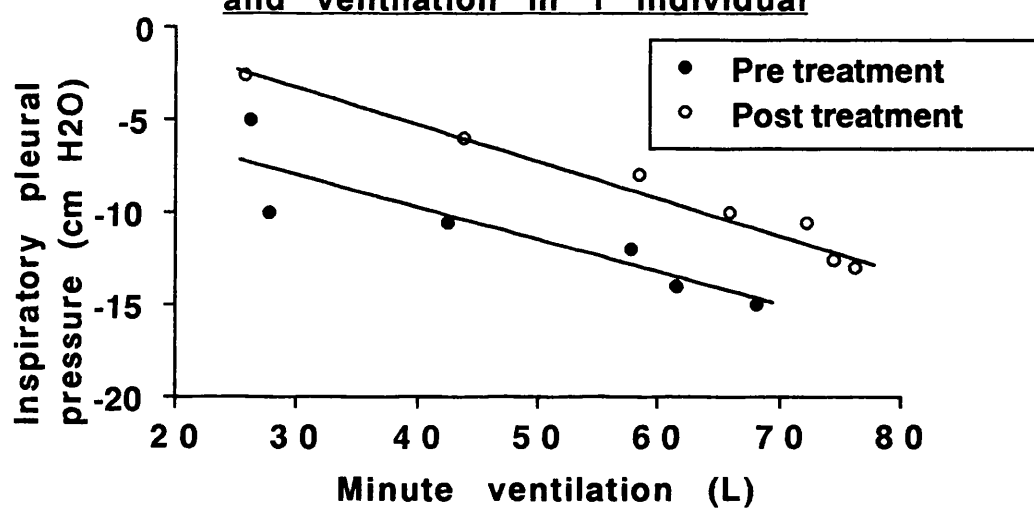


Table 12.3

Changes in ventilation, pleural pressure and breathlessness during isocapnic hypoxia

|         | V <sub>e</sub> (l/min) |      | P <sub>pl</sub> (cmH <sub>2</sub> O) |      | IES(Borg scale) |      |
|---------|------------------------|------|--------------------------------------|------|-----------------|------|
| Patient | pre                    | post | pre                                  | post | pre             | post |
| 1 Start | 17.5                   | 21.2 | -7.0                                 | -5.5 | 0               | 0    |
| End     | 19.7                   | 24.8 | -13.0                                | -11  | 7               | 7    |
| 2 Start | 27.6                   | 23.2 | -9                                   | -4   | 3               | 3    |
| End     | 48.1                   | 53.8 | -7                                   | -9   | 5               | 6    |
| 3 Start | 31.2                   | 28.4 | -16                                  | -12  | 1               | 3    |
| End     | 53.8                   | 52.2 | -25                                  | -22  | 6               | 9    |
| 4 Start | 12.4                   | 12.9 | -22                                  | -24  | 0               | 0    |
| End     | 26.3                   | 23.2 | -24                                  | -25  | 8               | 7    |
| 5 Start | 20.1                   | 19.8 | -12                                  | -5   | 0               | 0    |
| End     | 23.2                   | 20.2 | -10                                  | -8   | 0.5             | 0.5  |
| 6 Start | 28.1                   | 31.3 | -13                                  | -10  | 0               | 0.5  |
| End     | 47.6                   | 54.8 | -21                                  | -15  | 9               | 7    |

**Table 12.4**

**Changes in ventilation, pleural pressure and breathlessness during progressive hypercapnia**

| Patient | Ve(L/min) |      | Ppl(cmH <sub>2</sub> O) |       | IES(Borg scale) |      |
|---------|-----------|------|-------------------------|-------|-----------------|------|
|         | pre       | post | pre                     | post  | pre             | post |
| 1 Start | 20.2      | 22.1 | - 6                     | -4.5  | 3               | 0.5  |
| End     | 23.7      | 27.6 | -11.5                   | -10.5 | 7               | 7    |
| 2 Start | 26.3      | 25.6 | - 5                     | -2.5  | 3               | 3    |
| End     | 68        | 76.3 | -15                     | -13   | 7               | 7    |
| 3 Start | 31.3      | 33.2 | -15                     | -11   | 4               | 3    |
| End     | 51.8      | 61.7 | -25                     | -22   | 9               | 9    |
| 4 Start | 15.1      | 11.1 | -25                     | -20   | 0.5             | 0.5  |
| End     | 39.6      | 37.1 | -33                     | -20   | 9               | 7    |
| 5 Start | 22.1      | 18.3 | -10                     | -5.5  | 2               | 0    |
| End     | 51.7      | 48.4 | -14                     | -15   | 7               | 5    |
| 6 Start | 32.1      | 32.6 | -10                     | -11   | 3               | 2    |
| End     | 52.4      | 65   | -28                     | -25   | 7               | 9    |



Table 12.5

Mean inspiratory flow during CO<sub>2</sub> rebreathes (L/sec)

| Patient | Pre   |      | Post  |      |
|---------|-------|------|-------|------|
|         | Start | End  | Start | End  |
| 1       | 0.99  | 1.11 | 1.22  | 1.19 |
| 2       | 1.01  | 2.83 | 1.04  | 3.1  |
| 3       | 1.16  | 2.12 | 1.28  | 2.45 |
| 4       | 0.48  | 0.94 | 0.50  | 0.99 |
| 5       | 0.84  | 1.89 | 0.82  | 2.0  |
| 6       | 1.36  | 2.16 | 1.32  | 2.6  |

Table 12.6

Expiratory abdominal activity (cm H<sub>2</sub>O) during CO<sub>2</sub> rebreaths deviation from baseline

| Patient | Pre   |     | Post  |     |
|---------|-------|-----|-------|-----|
|         | Start | End | Start | End |
| 1       | 1.5   | 3   | 1     | 2.5 |
| 2       | 3.5   | 7   | 0     | 2   |
| 3       | 0     | 0   | 0     | 0   |
| 4       | 0     | 1   | 0     | 0   |
| 5       | 0     | 8   | 0     | 1.5 |
| 6       | 0     | 11  | 0     | 5   |

Table 12.7

Peak ventilation before expiratory abdominal activity (L/min)

| Patient | Pre              | Post             |
|---------|------------------|------------------|
| 1       | 20               | 25               |
| 2       | 26               | 72               |
| 3       | No abdo activity | No abdo activity |
| 4       | 52               | No abdo activity |
| 5       | 22               | 43               |
| 6       | 32               | 49               |

**Table 12.8**

**The IES/Ve slopes during isocapnic hypoxia and progressive hypercapnia  
(Borg scale units/L)**

(Values in parentheses indicate R<sup>2</sup> of slope)

| Patient | IES/Ve(Hypoxia) |                | IES/Ve(Hypercapnia) |                |
|---------|-----------------|----------------|---------------------|----------------|
|         | Pre             | Post           | Pre                 | Post           |
| 1       | 0.61<br>(0.18)  | 0.73<br>(0.54) | 0.67<br>(0.36)      | 0.77<br>(0.43) |
| 2       | 0.16<br>(0.89)  | 0.08<br>(0.84) | 0.08<br>(0.89)      | 0.07<br>(0.67) |
| 3       | 0.24<br>(0.87)  | 0.23<br>(0.6)  | 0.17<br>(0.41)      | 0.21<br>(0.99) |
| 4       | 0.25<br>(0.9)   | 0.20<br>(0.88) | 0.25<br>(0.85)      | 0.28<br>(0.77) |
| 5       | 0.03<br>(0.08)  | 0.13<br>(0.22) | 0.13<br>(0.66)      | 0.15<br>(0.79) |
| 6       | 0.27<br>(0.69)  | 0.27<br>(0.8)  | 0.14<br>(0.51)      | 0.15<br>(0.61) |

Table 12.9

IES/O<sub>2</sub> and IESCO<sub>2</sub> slopes before and after oxitropium bromide

(Values in parentheses indicate R<sup>2</sup> of slope)

| Patient | IES/SaO <sub>2</sub> (Borg units/%) |                 | IES/P <sub>et</sub> CO <sub>2</sub> (Borg units/kPa) |                |
|---------|-------------------------------------|-----------------|------------------------------------------------------|----------------|
|         | pre                                 | post            | pre                                                  | post           |
| 1       | -0.58<br>(0.88)                     | -0.61<br>(0.84) | 1.04<br>(0.79)                                       | 1.66<br>(0.59) |
| 2       | -0.22<br>(0.88)                     | -0.11<br>(0.85) | 2.06<br>(0.93)                                       | 1.57<br>(0.79) |
| 3       | -0.52<br>(0.94)                     | -0.57<br>(0.87) | 1.14<br>(0.46)                                       | 1.82<br>(0.59) |
| 4       | -0.65<br>(0.84)                     | -0.27<br>(0.72) | 3.58<br>(0.96)                                       | 2.2<br>(0.93)  |
| 5       | -0.06<br>(0.44)                     | -0.03<br>(0.39) | 1.46<br>(0.63)                                       | 1.78<br>(0.95) |
| 6       | -0.66<br>(0.9)                      | -0.66<br>(0.92) | 1.31<br>(0.48)                                       | 2.35<br>(0.88) |

**Table 12.10**

**Ve/SaO<sub>2</sub> and Ve/P<sub>et</sub>CO<sub>2</sub>slopes before and after oxitropium bromide**

(Values in parentheses indicate R<sup>2</sup> of slope)

| Patient | Ve/SaO <sub>2</sub> (L/%) |                 | Ve/P <sub>et</sub> CO <sub>2</sub> (L/kPa) |                 |
|---------|---------------------------|-----------------|--------------------------------------------|-----------------|
|         | pre                       | post            | pre                                        | post            |
| 1       | -0.12<br>(0.1)            | -0.57<br>(0.7)  | 0.84<br>(0.63)                             | 1.55<br>(0.71)  |
| 2       | -1.32<br>(0.92)           | -1.34<br>(0.87) | 24.4<br>(0.94)                             | 20.9<br>(0.95)  |
| 3       | -1.96<br>(0.88)           | -1.66<br>(0.62) | 6.05<br>(0.93)                             | 8.69<br>(0.59)  |
| 4       | -3.23<br>(0.93)           | -1.31<br>(0.74) | 12.44<br>(0.84)                            | 5.45<br>(0.66)  |
| 5       | 0<br>(0)                  | 0<br>(0)        | 11.37<br>(0.92)                            | 10.02<br>(0.84) |
| 6       | -1.83<br>(0.75)           | -2.07<br>(0.82) | 9.2<br>(0.91)                              | 12.21<br>(0.87) |

## Discussion

This experiment has demonstrated that PEEPi is present during spontaneously breathing in patients with COPD, and that the magnitude of PEEPi falls after bronchodilator. The occurrence of PEEPi is well recognised in mechanically ventilated (IPPV) patients with COPD though the technique of measurement usually employed measures static PEEPi. The measurement of static PEEPi during spontaneous breathing is difficult particularly when the subjects are dyspnoeic at rest as it requires complete relaxation of the respiratory muscles against a closed shutter at the end of a normal expiration. For this reason dynamic PEEPi was measured.

The presence of PEEPi during resting breathing might be expected in patients with severe COPD whose expiratory flows are close to maximum during resting tidal breathing. As discussed previously in this thesis FRC in patients with severe COPD may be dynamically determined, inspiration being initiated before the elastic recoil of the respiratory system is reached. Under these circumstances PEEPi represents the residual elastic recoil pressure of the chest wall and lung still present to drive expiration at the onset on inspiratory muscle activity. Reductions in FRC might therefore be expected to be accompanied by falls in PEEPi which represents an indirect measure of dynamic hyperinflation. However falls in PEEPi were not quantitatively related to the reductions in FRC which occurred. This lack of relationship to falls in FRC is surprising and there are several possible explanations. Only part of the hyperinflation seen in long standing COPD is dynamically determined, the remainder being dependent on static forces. Compensatory changes in respiratory system compliance may have occurred as a result of the long standing hyperinflation, (though this would be extremely difficult to show experimentally). Increases in respiratory system compliance would diminish PEEPi and thus reduce the work

of breathing. Alternatively methodological reasons may be responsible. The FRC measured in the body plethysmograph is the mean of 3 breaths, whereas the PEEPi measurement is the mean value determined over 10 breaths. Also the position of FRC may be different between the 2 measurements. As has been discussed earlier inspiratory capacity is less in the plethysmograph than in the relaxed posture adopted during helium dilution FRC measurements.

Increases in FEV1 or falls in airways resistance which occur in this group of patients in response to anticholinergic bronchodilators might also be expected to relate to falls in PEEPi. As discussed earlier the FEV1 is a relatively poor guide to airflow resistance during tidal breathing. Changes in airways resistance may have been a better correlate of reductions in PEEPi following bronchodilator but this was not measured in this experiment.

The lack of relationship between PEEPi and measures of airflow obstruction is in contrast to previous workers (Haluszka et al 1990) who found a relationship between PEEPi and pulmonary flow resistance in a large retrospective study of COPD patients. This group also demonstrated a weak relationship ( $r = 0.31$ ) between PEEPi and FRC measured by the helium dilution technique. The values of PEEPi dyn found in this study are in line with those reported by Haluszka but are lower than in studies which have measured PEEPi stat as expected. Petrof and coworkers (1990) found that PEEPi dyn represented on the average 57% of PEEPi stat. The reason for the difference is that PEEPi stat measures the mean regional PEEPi after all regional pressure differences have equilibrated whereas PEEPi dyn measures the lowest regional PEEPi (Haluszka 1990).

Both resting PEEPi and breathlessness fell variably after bronchodilator. The reductions in PEEPi may be responsible for some of the reductions in

breathlessness. PEEPi imposes an inspiratory threshold load which must be overcome before airflow can begin. Reducing this threshold load will reduce the work required to breathe with reductions in neural activation which are closely allied to reductions in perceived breathlessness. Other authors have examined the role of PEEPi in the sensation of breathlessness in different ways. Petrof (1990) examined the effect of CPAP on patients with COPD during weaning from mechanical ventilation, finding reductions in dyspnoea following the application of CPAP. O'Donnell (1988) examined the effect of CPAP on the sensation of breathlessness during exercise in COPD and in normals finding reduced breathing effort in COPD patients with an increase in normal individuals. The application of CPAP counterbalances the threshold load imposed by PEEPi and may reduce breathlessness by this mechanism. An additional effect of the application of CPAP is a reduction in the pleural pressure swings during tidal breathing. A similar reduction in pleural pressure swings during resting tidal breathing was seen after the administration of bronchodilator. The reduction in pleural pressure following bronchodilator administration is a reflection of the reduction in both airways resistance and a reduction in dynamic hyperinflation. Reductions in dynamic hyperinflation result in reduced chest wall recoil, as the end expiratory lung volume approaches the relaxation volume of the chest wall, whilst a reduction in airways resistance means lower intrathoracic pressures are required for a given airflow.

#### Changes in PEEPi during stimulated breathing

The levels of 'PEEPi' increased throughout the stimulated breathing runs. However the reliable measurement of PEEPi requires that expiration be passive ie that no expiratory abdominal muscle activity takes place. Whilst the intrathoracic pressures at the onset of inspiratory muscle activity



became more positive later in the tests greater abdominal muscle activity was present during the later stages of the stimulated breathing runs. The magnitude of the gastric positive expiratory pressure swings were smaller following oxitropium bromide but the positive pressure swings were still large in comparison to the 'PEEPi' measurements at higher ventilations. Thus quantitative PEEPi measurements at higher ventilations using this model in these patients are invalid and only qualitative changes can be inferred and then the results should be treated with caution. It should be noted that positive expiratory activity in COPD patients does not always result in 'PEEPi'. In patient 2 no PEEPi was present despite 3.5cm H<sub>2</sub>O positive gastric pressure swings. Despite the inability to accurately measure PEEPi in the presence of expiratory muscle activity, other work suggests that in patients with severe COPD PEEPi will increase at higher ventilations because FRC tends to rise on exercise in these individuals (Stubbing 1980, Grimby 1970).

Although abdominal expiratory muscle activity confounds the measurement of PEEPi, its presence is an indicator of expiratory muscle effort which may itself be an important determinant of dyspnoea. Oxitropium reduced or abolished abdominal activity where present during resting breathing, and reduced the abdominal contribution to expiratory pleural pressure swings at high ventilations. Despite the reduction in abdominal activity it had no effect on the expiratory pleural pressures either at rest or peak ventilation. This finding suggests that abdominal expiratory activity is a more important determinant of breathlessness than thoracic expiratory activity, and suggest that bronchodilators improve the efficiency of breathing by obviating the need for expiratory accessory muscle use. The administration of bronchodilator increased mean inspiratory flows at similar levels of breathlessness again suggesting that breathing has become

more efficient. This finding is consistent with the higher peak inspiratory flows noted during the larger oxitropium experiment and may be explained similarly; the reductions in lung volumes which we measured increase the efficiency of the inspiratory muscles by shortening resting diaphragmatic length. Also reductions in airways resistance increase the airflow for a given muscle activity.

#### The rate of change of sensation with ventilation

There was no change in the slope of the IES/ $V_E$  relationship following bronchodilator, neither was there any difference in the slopes of the IES/ $V_E$  plots for hypercapnic and hypoxic experiments. This suggests that the rate of change of sensation with ventilation is an inherent characteristic of an individual, unaffected by stimulus or mechanical factors. This data contrasts with work in normal individuals during loaded breathing experiments (Clague 1992) which have shown that the degree of hypoventilation induced by a resistive load is inversely related to the rate of increase of sensation with ventilation during unloaded breathing. The reason for the differing findings may be the relatively small changes in airways resistance compared to 'background' or pre bronchodilator values induced by the bronchodilator compared to the larger relative increases induced by resistive breathing in normal individuals. The similar increases in sensation with both stimuli also contrasts with other work which have suggested that hypercapnia is a 'dyspnogen' inducing higher levels of breathlessness for a given ventilation than exercise.(Chonan 1990). It is possible that hypoxaemia has similar modulating effects on the sensation of dyspnoea as hypercapnia. In summary this experiment has shown that bronchodilators induce complex changes in lung mechanics, reducing airways resistance and allowing

increases in ventilation. Reductions in airways resistance result in falls in lung volume, reduced pleural pressure swings, delayed onset of abdominal muscle activity and reductions in PEEPi. All of these may be important determinants of the sensation of breathlessness with no single factor likely to be dominant.

## CONCLUDING REMARKS

I have presented data in this thesis showing that bronchodilators, both anticholinergic and beta agonist relieve dyspnoea and improve exercise performance in patients with COPD. These improvements were not predicted by changes in spirometry, very small changes being associated with similar functional improvements to much larger ones. It had been anticipated at the outset of the studies that the improvements in exercise tolerance and breathlessness which had been shown by previous authors in response to different classes of bronchodilator in the absence of spirometric change could be explained by falls in end expiratory lung volume with consequent improvements in respiratory muscle geometry and thus efficiency. This did not prove to be the case, and only those patients with spirometric reversibility showed significant changes in resting static lung volumes. Similarly the increased breathlessness seen following histamine induced bronchoconstriction was not closely related to alterations in resting end expiratory lung volume.

While significant falls in airways resistance of similar magnitude occurred in the spirometrically reversible and irreversible groups, these falls were not quantitatively related to improvement in breathlessness or exercise tolerance.

An incidental observation made during the airways resistance measurements may provide an indication for the lack of relationship between changes in lung volume and reductions in breathlessness. The increased breathing frequency required for these measurements resulted in an increase in end expiratory lung volume. Thus changes in resting static lung volumes are not a good measure of changes occurring during increased activity, when breathing frequency is increased. Measurement of these dynamic changes is difficult, but changes in airways resistance may provide an easily

measurable variable which indicates changes in these more elusive mechanical parameters.

Further indications of the dynamic control of FRC in the patients with severe COPD are provided by the changes measured in the stimulated breathing experiments. Patients with severe COPD show intrinsic PEEP, the magnitude of which increased as breathing frequency increased during the stimulated breathing experiments. PEEPi provides an indirect measure of the dynamic hyperinflation occurring at increased breathing frequencies. The magnitude of PEEPi was reduced by bronchodilator, suggesting that the increases in lung volume on exercise are less following bronchodilator. Oxitropium bromide also reduced the pleural pressure swings at equivalent levels of ventilation, and reduced the level of abdominal muscle activity, both of which may offer further explanations for the reductions in breathlessness brought about by bronchodilator.

Although changes in forced expiratory flows did not relate to improvements in breathlessness or exercise tolerance, inspiratory flows were correlated with improvements in end of walk breathlessness. This may be because increased ventilation in patients with relatively fixed expiratory flows are dependent on increases in breathing frequency. This can only be achieved by shortening inspiratory time, and the degree to which this can be achieved is dependent on maximal inspiratory flow rates.

While alterations in lung mechanical measurements were in general modest, they were nevertheless in a 'beneficial' direction ie increases in flows and reductions in airways resistance and end expiratory lung volume. In contrast resting oxygen saturation fell slightly following the anticholinergic bronchodilator and was unaltered following salbutamol. Similarly oxygen saturations during the walk were unaltered by either

bronchodilator. These findings suggest that changes in oxygen saturation are not an important factor in the genesis of dyspnoea in comparison to mechanical factors.

There are several important negative findings resulting from the work presented in this thesis. X ray planimetry, despite having theoretical advantages for the measurement of lung volume in patients with airflow obstruction, has been shown to be too unreliable for routine use, and therefore has no place in the assessment of individual patients. It may still have a place in population studies where no other lung volume data is available.

Trapped gas volume has also been shown to be a poor measure of response to inhaled bronchodilator treatment. Subsequent studies proposing its use should be checked for methodological errors resulting from prolonged time constants for pressure equilibration and gas mixing.

Conventional complex variables derived from the expiratory limb of the flow volume loop conferred no advantage over simple spirometry in the prediction of functional response. Indeed those portions of the flow volume loop which are said to be 'effort independent' showed no change following bronchodilator.

The measurement of mouth occlusion pressure as an measure of neuromuscular drive and as a correlate of breathlessness proved disappointing.

Measurement of  $P_{0.1}$  as a measure of response to bronchodilators in patients with severe COPD is flawed as these individuals often have significant degrees of PEEPi and their end expiratory lung volume may change in response to bronchodilator. For these reasons occlusion pressure measurement probably has no place in the routine clinical assessment of

patients with COPD and physiological studies using it as a measure of respiratory drive in these patients should be treated with caution.

#### Indications for further studies

Further work is required on the effect of bronchodilators on the dynamic aspects of breathing. Larger studies are required to properly assess the effect of alterations in PEEP<sub>i</sub>, breathing pattern and pleural pressure swings following bronchodilator. Further studies using static lung volumes will probably not yield any further useful data. However measurement of lung volumes during stimulated breathing, either progressive hypercapnia or exercise, may be useful in directly assessing the role of dynamic hyperinflation in breathlessness in COPD. Simultaneous measurement of PEEP<sub>i</sub> will allow assessment of the use of PEEP<sub>i</sub> as an indirect measure of hyperinflation in COPD. There may be some value in using other models which reduce the work of breathing without altering airway calibre. Studying the effect of breathing low density gas mixtures on breathlessness and dynamic lung mechanics may be such a model.

#### Implications in the treatment of COPD

Severe chronic obstructive pulmonary disease is a condition for which only symptomatic treatment is available. Therapeutic trials of bronchodilator using only conventional lung function tests appear to be worthless except as a diagnostic test to exclude asthma.

The clinical application of the 6 minute walking test is limited by the learning effect. However assessments of breathlessness following bronchodilator trial should be routine. Significant placebo effect could be excluded by the inclusion of a placebo trial in bronchodilator trials and by performing these studies in a single blind manner.

Clinically we should be more prepared to believe our patients' assessment of their own breathlessness which includes a full assessment of the mechanical impediment to breathing (by the patients brain and brainstem!) and place less reliance on lung function tests which can only address individual aspects of a multifactoral process.



## APPENDIX I

### Equipment

#### Airway occlusion Valve

During the rebreathing experiments a manually operated helium balloon valve Series 9300 produced by Hans Rudolf Inc, Kansas, USA was used to produce airway occlusion for the occlusion pressure measurements. Occlusion pressure was otherwise measured using the same balloon system operated by a computer (Amstrad 1640). The balloon deflation time was 60 msec.

#### Carbon dioxide scrubber

The CO<sub>2</sub> scrubber was constructed with a fan from an obsolete CPAP machine (Air Control Installation (Chard) Ltd, Somerset, UK) equipped with a rheostat to regulate the fan speed. the efficiency of the seals on the device was checked by inflating a 7 litre anaesthetic bag connected to the scrubber. No deflation of the bag occurred over 5 minutes at normal operating fan rates.

#### Chart recorders

2 types of chart recorder were used, during the rebreathing experiments pressure flow and volume were recorded onto a Gould 2000 series chart recorder.

For the plethysmograph validation experiments pressures and balloon validation experiments pressures were recorded onto a Schwarzer Uniscript UD 210 chart recorder

### End tidal CO2 analyser

Eliza CO2 analyser produced by Gambro Engstrom AB, Sweden.

### Pulse oximeter

The Biox 3700e produced by Biox Ohmeda UK Ltd.

### Pressure measurements

Several pressure transducers were used. During the rebreathing experiments mouth pressure, oesophageal pressure and gastric pressure were measured using P23XL pressure transducers and Gould transducer amplifiers (Model 13-4615-50), Gould UK Ltd. Oesophageal pressure for the plethysmographic measurements was measured using a Validyne MP45 pressure transducer produced by the Validyne Corporation, USA.

### Oesophageal balloons

Oesophageal and gastric manometry was performed using balloon catheter systems produced by PK Morgan Ltd connected to Gould pressure transducers.

### Flow measurements

Respiratory flow was determined by using heated Fleisch pneumotachnographs Nos 2 and 3. The signal was integrated using a Gould integrator amplifier (Model 13-4615-70) to provide a volume signal

### Instrumentation recorder

For the plethysmograph validation experiments mouth, oesophageal and box pressures were recorded onto magnetic tape using a Racal Store 7D FM tape recorder, Racal Electronics, Southampton UK

#### Helium dilution lung volume equipment

Helium dilution lung volume measurements were made using a PK Morgan Transfer Test Equipment model B helium analyser attached to an 8L rolling seal spirometer.(PK Morgan Ltd, Chatham, Kent)

#### Plethysmographic lung volumes

Plethysmographic lung volume measurements were made using a PK Morgan constant volume body plethysmograph using Version 3 software run on a Samsung 6000 286 microcomputer

#### Flow volume loops

Flow volume loops were performed on a PK Morgan 12L rolling seal spirometer using Version 3 software run on a Samsung 6000 286 microcomputer.

#### Histamine Dosimeter

The dosimeter was custom built and powered by compressed air. The nebuliser was manufactured by System 22. The nebulisation time of the dosimeter was set to 2 seconds to begin immediately after the onset of inspiration.

#### X-Y Plotter

The XY plotter used for the verification of the plethysmograph was a Bryans 26700 fast response plotter, Bryans Instruments UK

#### Phase correction

The phase correction for the oesophageal balloon measurements in the plethysmograph was performed using a C3M digital signal processing board based on the TMS 32010 chip attached to an Opus PC4 286 microcomputer.

## APPENDIX II

### Calibration Procedures

Barometric pressure and ambient temperature were entered into the computers which derived the flow volume loops and plethysmographic measurements.

#### End tidal CO<sub>2</sub> analyser

The end tidal CO<sub>2</sub> analyser was calibrated monthly using Engstrom CO<sub>2</sub> calibration gas certified to  $\pm 0.05\%$

#### Pressure Transducers

For the rebreathing experiments after balancing the transducer amplifiers the pressure transducers were calibrated to produce a particular deflection on the chart recorder using a water manometer. Calibration was tested with several pressures in the range required. The balance was checked by halving or doubling the gain to produce half or double the deflection on the chart recorder.

#### Pneumotachograph

The pneumotachograph used during the rebreathing experiments was allowed to warm up to operating temperature and then a precision 1L syringe was used to draw air through the pneumotachograph at varying flow rates. The signal was integrated and the volume signal calibrated. Mean inspiratory flow, and volume measurements were determined from the chart recorder.

#### Helium dilution equipment

The helium analyser was calibrated daily using gas of known composition Calibgas, Cryoservice Ltd, Worcester, UK

### Body plethysmograph

The computer was calibrated for flow, mouth pressure and box pressure daily.

Flow- The mouthpiece pneumotachograph was calibrated using a precision 3L syringe to draw air through the assembly at various flow rates. This data was used by the computer to create a "look up" table of the flows thus overcoming problems the of a linearity of the pneumotachograph over a wide range of flow rates. The calibration was checked by drawing air through the pneumotachograph with the 3L syringe at various rates and was only accepted if the volume measured was 3L +/- 200ml.

Mouth pressure- The mouth pressure transducer was calibrated using a water filled manometer and was verified in a similar fashion

Box Pressure- The box pressure transducer was calibrated using a sinusoidal 100ml pump.

### Computerised occlusion pressure measurement

The computer was calibrated daily by connecting a water manometer to the plethysmograph mouth pressure transducer to measure negative pressure. The calibration was checked over a range of values weekly to ensure linearity of the system.

### X ray planimeter

The planimeter and computer were calibrated daily using 2 points of known coordinates on the planimeter screen. The outputs from the potentiometers on the tracing arm were checked at the beginning and end of the study by the manufacturer.

## APPENDIX III

### Validation of methods used

#### Pressure Transducers

The response times of the P23XL transducers were determined by inserting the free end of non compressible pressure tubing inside an inflated balloon which was then burst (the "pop" test) The response time was the time taken to return to zero on the chart recorder running at 100mm/s. This was repeated 6 times, the mean response time was 0.06seconds (SD 0.006)

#### Circuit resistance

The inspiratory and expiratory resistance of the circuit used in CO<sub>2</sub> rebreathing and in isocapnic hypoxemic breathing was measured using a rotameter (KDG 2000 flowmeter, Mercury Electronics Ltd, Glasgow). The pressure drop across the circuit was measured using a Validyne MP45 differential pressure transducer at various flow rates.

At 60L/min

|                        |                           |
|------------------------|---------------------------|
| Inspiratory resistance | 1.3cmH <sub>2</sub> O/L/s |
| expiratory resistance  | 1.2cmH <sub>2</sub> O/L/s |

#### Helium Dilution lung volumes

The linearity of the system was checked by adding to the spirometer a 4 to 1 mixture of helium and oxygen, then emptying the spirometer and sealing the system. Air was added to the system in 1L aliquots and the system dead space calculated. There was no change in the calculated dead space up to an added volume of 5L (table A.1).

Table A.1  
Validation of linearity of helium dilution equipment

| Volume of air added<br>(L) | Helium concentration<br>(%) | Calculated deadspace<br>(L) |
|----------------------------|-----------------------------|-----------------------------|
| 0                          | 15.64                       | -                           |
| 1                          | 12.12                       | 3.44                        |
| 2                          | 9.81                        | 3.36                        |
| 3                          | 8.28                        | 3.37                        |
| 4                          | 7.12                        | 3.34                        |
| 5                          | 6.24                        | 3.32                        |
| 6                          | 5.5                         | 3.5                         |

### Verification of dosimeter

The output of the dosimeter was verified using a Malvern instruments 2600C aerosol droplet and particle sizer. This was performed at the Department of Medical Physics, The Royal Free Hospital, London.

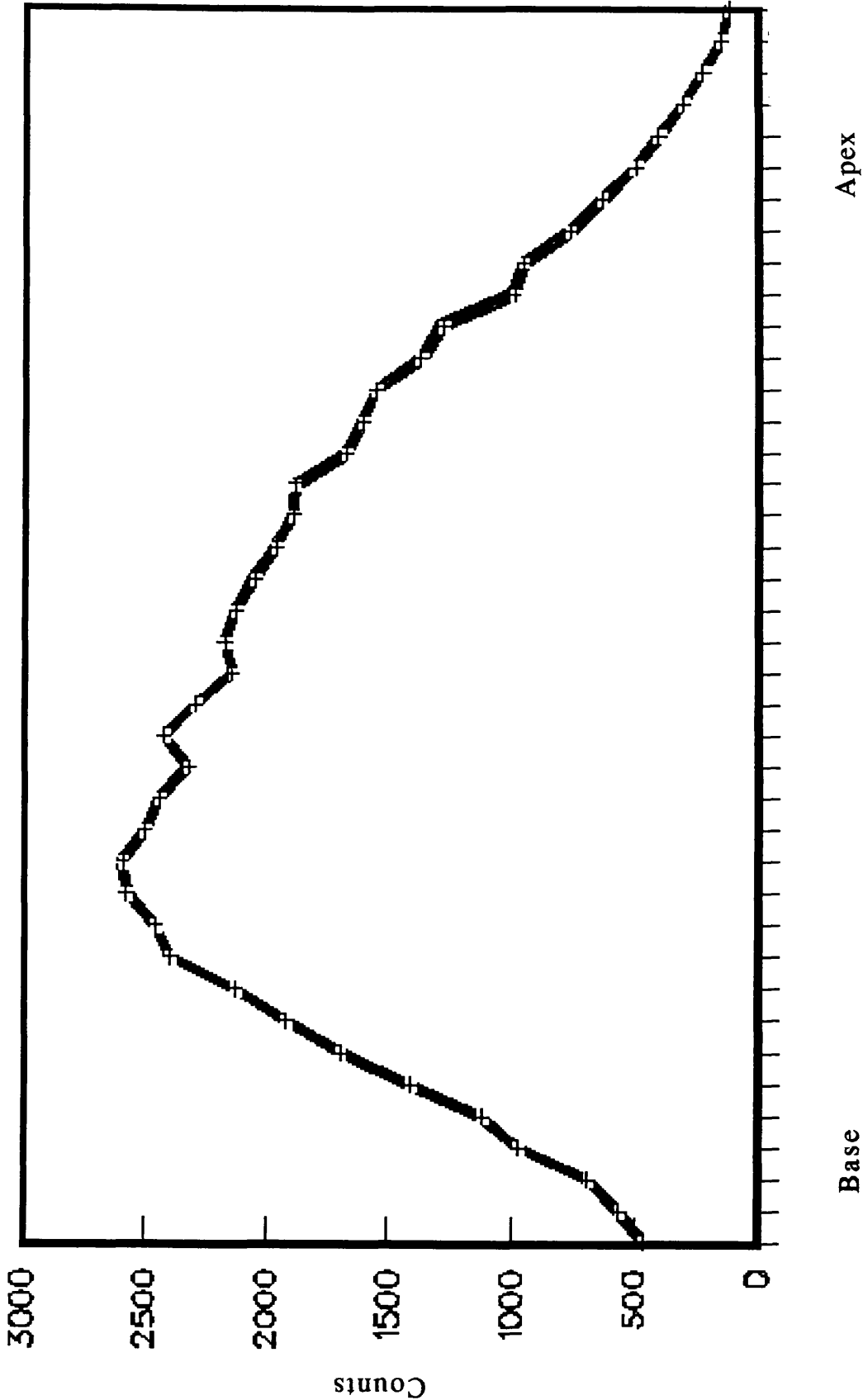
Results of the analysis are given in table A.2. The mass median diameter of the particles generated by the nebuliser was 5.2 microns, (geometric SD 9.6/5.3).

The deposition pattern of the droplets was assessed in a normal volunteer using a radioisotope labelled DTPA technique. This was again performed by the Royal Free Hospital. The deposition pattern was uniform throughout the lung (Fig A.1).



Figure A.1

The deposition pattern of the nebuliser output in the lung



## The effect of additional upper airway support on plethysmographic lung volume measurements

### Introduction

Stanescu (1982) and Shore (1982) have shown that in COPD body plethysmography can result in higher lung volume measurements when mouth pressure rather than oesophageal pressure is used to estimate alveolar pressure during panting manoeuvres against a closed shutter. They have shown that the magnitude of the overestimate of lung volume is related to the distensibility of the upper airway. Rodenstein et al (1983) have shown that bypassing the extra thoracic airway with an endotracheal tube abolishes these overestimates when airway opening pressure is used for lung volume estimations in body plethysmography. Clements in 1959 in his original description of the interrupter method of determining pulmonary resistance noted that resistance measurements were higher when the upper airway was distensible. Llistro (1989) has shown recently that airways resistance measurements made by the interrupter method are lower when support is given to the floor of the mouth in addition to the cheeks. Plethysmographic lung volume measurements are conventionally made with cheek support alone leaving the sub mandibular and upper neck soft tissues unsupported and acting as a shunt compliance. I have examined the effect of additional upper airway support on lung volume estimations by body plethysmography in COPD.

### Methods

28 patients with severe COPD [age(SD) 62.5(7.8)years, FEV1 0.86(0.29), percent predicted FEV1 29(9)] were recruited from the out patient clinic at Fazakerley Hospital. Three lung volume measurements were made with conventional cheek support and three with additional floor of the mouth

Figure A.2

The position of the hands during conventional plethysmographic measurements with cheek support alone

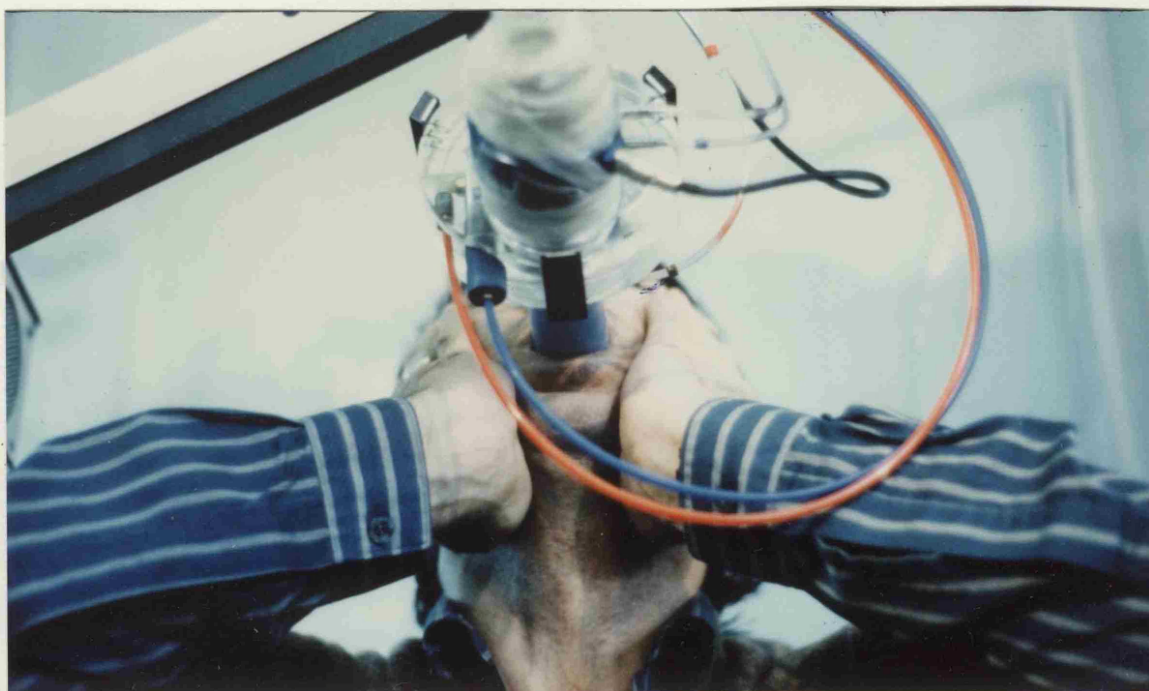
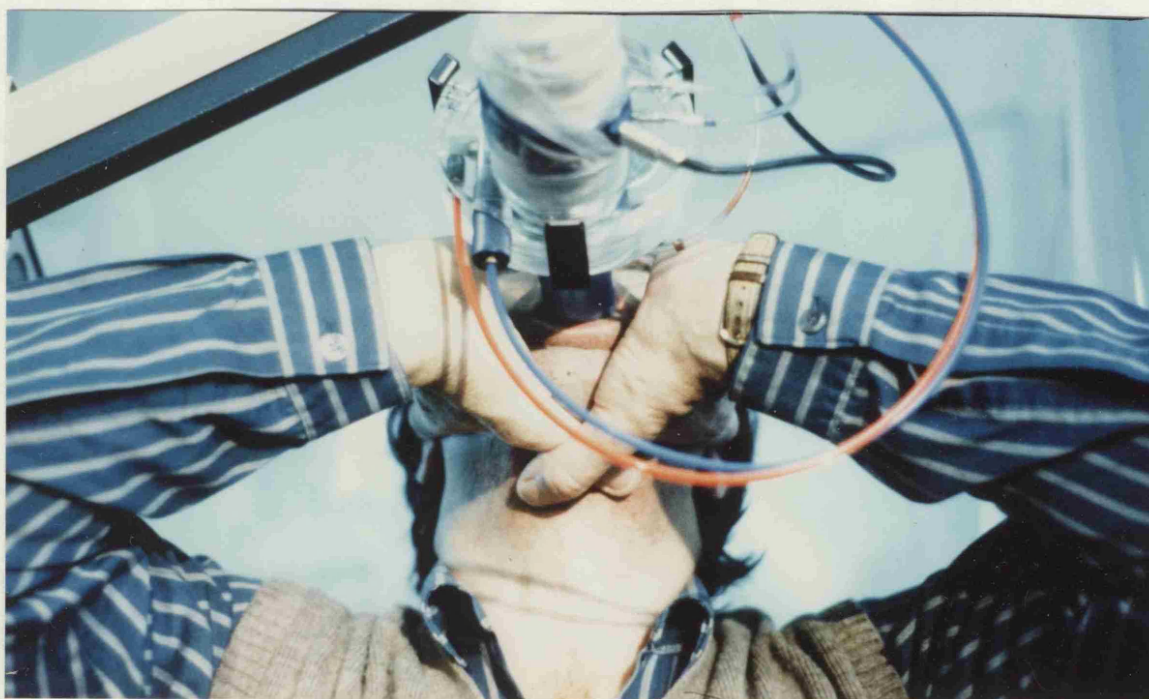
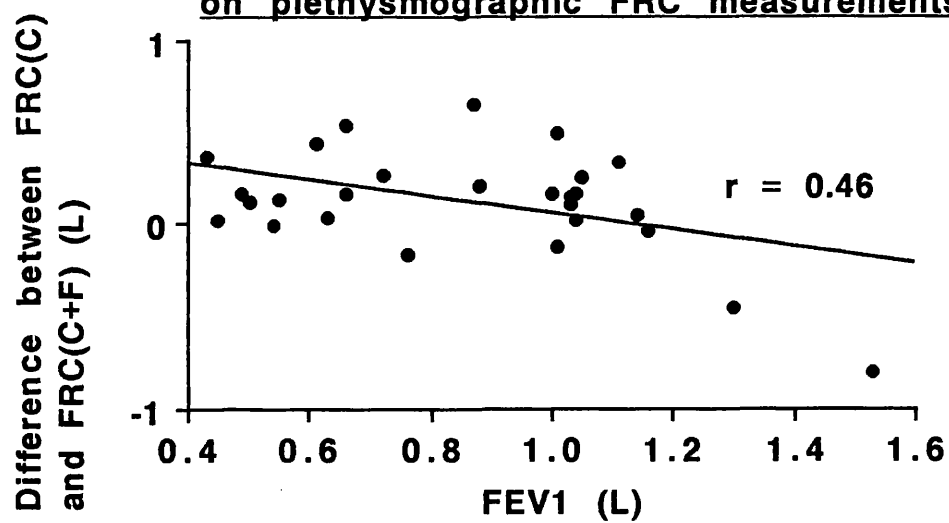


Figure A.3

The position of the hands to provide additional floor of mouth support during plethysmographic measurements



**Figure A.4**    Effect of additional upper airway support  
on plethysmographic FRC measurements



support (Figures A.2 and A.3). Measurements were performed with and without additional support in random order. Panting frequency for all measurements was 1Hz timed by a metronome. All measurements were performed in a constant volume variable pressure body plethysmograph the calibration of which is described elsewhere. Statistical analysis was by means of a students T test for paired data.

### Results

Support to the floor of the mouth in addition to the cheeks resulted in a small but significant reduction in lung volume measurements. The FRC with cheek support alone was [mean (SE)] 6.37 (0.28)L, and with additional upper airways support 6.25 (0.29) L ( $p < 0.02$ ). The magnitude of the difference between the measurements correlated significantly with FEV 1  $R = -0.46$  ( $p < 0.02$ ) (figure A.4). However there was no correlation between the difference and percent predicted FEV 1 or with airways resistance. One patient has been excluded from the analysis. In her case FRC determined using cheek support alone exceeded that derived from cheek and upper airways support method by in excess of 3 litres. On review of her mouth pressure/box pressure plots excessive looping was evident on the cheek support alone measurements.

### Discussion

We have shown that additional upper airways support results in small but significant reductions in plethysmographic lung volume estimations compared to those derived when only conventional cheek support is given. This result is at variance with previous studies (Begin 1984 and Rodenstein 1983) which have suggested that when panting frequencies of less than 1 Hz are employed overestimates of lung volume using mouth pressure do not occur. The difference between this study and previous work may be the severity of

airflow obstruction of our patients, and also their greater age and therefore more floppy upper airway due to loss of connective tissue. The difference between measurements using cheek support and cheek and additional upper airways support, though small, nevertheless represents 12% of the measured difference between FRC measured by helium dilution and by body plethysmography (see proceeding chapters).

The relationship between declining FEV<sub>1</sub> and the magnitude of the difference between the two techniques may be explained by the upper airway acting as a shunt compliance during panting manoeuvres against a closed shutter. The airway expands and contracts allowing gas flow to occur between intra-thoracic airway and mouth. Provided no airflow obstruction exists then no pressure drop between alveolus and mouth occurs. However in the presence of airflow obstruction the pressure drop between alveolus and mouth is proportional to the magnitude of the resistance across which the flow occurs. Data from this study agrees with the work of Rodenstein (1982) who showed that the overestimates in measured thoracic gas volume using airway opening pressure induced by artificial airway stenoses could be abolished by using an endotracheal tube to bypass the upper airway. Stanescu and co authors (1982) also showed a relationship between the difference between thoracic gas volume estimations using oesophageal pressure and those using mouth pressure and the degree of airway obstruction in asthmatics.

The relationship between airflow obstruction (FEV<sub>1</sub>) and the magnitude the difference between TGV cheek and TGV cheek and floor has implications when making plethysmographic lung volume estimations in severely obstructed patients, and suggests that support to the extra-thoracic airways should be routine in these subjects.

## The effect of panting frequency on plethysmographic lung volume measurements in COPD

### Introduction

Previous studies have demonstrated failure of the plethysmograph at higher panting frequencies in both normal individuals and in asthmatic subjects. Rodenstein examined the effect in COPD and found that higher lung volumes were derived from panting at frequencies in excess of 2Hz than with panting frequencies less than 1 Hz. In order to verify the accuracy of the lung volume measurements, and the changes following bronchodilator, I have measured lung volumes at 2 panting frequencies before and after bronchodilator.

### Methods

A subgroup of 6 patients was recruited from the larger oxitropium bromide study. All were familiar with the technique required for lung volume estimations by body plethysmography. In particular they were able to accurately match their panting frequency with the beats of an electronic metronome. All patients abstained from beta agonist bronchodilators for at least 6 hours, from anticholinergic medication for at least 12 hours and from oral bronchodilators for at least 24 hours prior to the study. Measurements were performed before and 15-20 minutes after 200mcg oxitropium bromide. FEV1 was measured on a rolling seal spirometer (best of 3 measurements) before and after the drug.

### Results

There was a tendency for the higher panting frequency to result in higher lung volume measurements (table A.3), but in this small number of patients this did not achieve statistical significance. The difference between the 2

panting frequencies was largest (in excess of 1.5L) in the individual with the lowest FEV1.

### Discussion

This small experiment confirms the findings of Rodenstein and emphasises the importance of maintaining low panting frequencies when making plethysmographic measurements in COPD.



Table A.3

The effect of panting frequency on plethysmographic lung volume measurements

| Patient   | Pre medication |           |          | Post medication |           |           |
|-----------|----------------|-----------|----------|-----------------|-----------|-----------|
|           | FEV1(L)        | FRC       | FRC      | FEV1 (L)        | FRC       | FRC       |
|           |                | 1Hz (L)   | 2Hz (L)  |                 | 1Hz (L)   | 2Hz (L)   |
| 1         | 1.24           | 8.81      | 9.31     | 1.55            | 7.78      | 7.18      |
| 2         | 0.37           | 6.47      | 8.26     | 0.47            | 6.53      | 10.78     |
| 3         | 0.86           | 5.82      | 7.08     | 1.15            | 4.49      | 4.88      |
| 4         | 0.89           | 4.29      | 4.4      | 1.32            | 3.48      | 3.55      |
| 5         | 1.27           | 5.82      | 5.13     | 1.62            | 4.33      | 4.01      |
| 6         | 0.86           | 5.96      | 6.02     | 1.02            | 5.03      | 5.36      |
| 7         | 0.55           | 7.15      | 7.37     | 0.76            | 6.39      | 6.72      |
| Mean (SE) | 0.86(.12)      | 6.33(.53) | 6.8(.65) | 1.13(.16)       | 5.43(.57) | 6.07(.93) |

## The difference between mouth and oesophageal pressure for the measurement of Thoracic Gas Volume

### Introduction

In order to verify the reductions in plethysmographic lung volumes following oxitropium bromide I have made measurements of lung volume derived from simultaneous measurements of mouth and oesophageal pressure before and after oxitropium bromide.

### Methods

In 4 of the patients who participated in the effect of panting frequency experiment an oesophageal balloon catheter system was inserted transnasally after anaesthetizing the nose and oropharynx with 4% lignocaine spray. The balloon was inserted to 45cm from the anterior nares into the stomach and was inflated with 0.5cc of air. It was withdrawn until a negative intrathoracic pressure swing was evident on sniffing, and then withdrawn a further 5cm so its entire was within the oesophagus. Tracheal and cardiac artefact were checked for and the balloon repositioned to minimise these if present. The balloon catheter was connected to a pressure transducer (Validyne MP 45). Mouth pressure, oesophageal pressure and box pressure were recorded onto a Schwarzer model UD210 chart recorder, and simultaneously recorded onto FM tape for subsequent analysis.

Slopes of mouth and oesophageal pressure against box pressure were made using a Bryans fast response XY plotter and the tangents of these slopes calculated. The response time of the system was checked as detailed below. The lags in the oesophageal balloon system were corrected for electronically using a C3M digital signal processor attached to an IBM compatible PC. By this technique the box pressure signal and oesophageal

pressure were in phase. 3 measurements were performed panting at 1Hz timed by a metronome while supporting the cheeks.

### Results

Because of the requirement for the oesophageal pressure transducer to be situated outside the box for technical reasons there were significant lags in the pressure response of the balloon catheter system. For this reason it was not possible to obtain quantitative measures of TGV. However it was possible to correct for phase lags between oesophageal pressure and box pressure using an electronic phase correction of 65msec. This allowed changes in the tangents to be reliably measured.

Both the mouth pressure and oesophageal pressure vs box pressure tangents increased after oxitropium bromide (table A.4)

### Discussion

I have assumed that changes in oesophageal pressure are a close approximation of alveolar pressure in a closed system, and that changes in oesophageal pressure are not subject to time constant artefact. This validation experiment suggests that the measured falls in lung volume were real and not artefactual due to alterations in the time constants for pressure equilibration between alveolus and mouth.

Table A.4

Measurement of TGV from mouth and oesophageal pressures

(Values quoted are Tan alpha values measured from  $P_{\text{box}}/P_{\text{mouth}}$  or  $P_{\text{oes}}$  plots)

| Patient | Pre drug |        | Post drug |        |
|---------|----------|--------|-----------|--------|
|         | Mouth    | Oesoph | Mouth     | Oesoph |
| 1       | 1.28     | 0.34   | 1.66      | 0.55   |
|         | 1.26     | 0.36   | 1.63      | 0.57   |
|         | 1.43     | 0.39   | 1.73      | 0.50   |
| 2       | 0.98     | 0.36   | 1.09      | 0.45   |
|         | 0.97     | 0.36   | 0.93      | 0.44   |
|         | 0.93     | 0.38   | 1.04      | 0.43   |
| 3       | 0.97     | 0.48   | 1.21      | 0.39   |
|         | 0.85     | 0.45   | 1.05      | 0.45   |
| 4       | 0.91     | 0.39   | 0.91      | 0.41   |
|         | 0.96     | 0.34   | 0.97      | 0.44   |
|         | 1.02     | 0.39   | 1.02      | 0.52   |

## Validation of computerised occlusion pressure measurements

### Methods

6 healthy normal volunteers were studied, 3 male and 3 female, mean age 26years (range 22-31years). Each subject breathed for 3 minutes on a mouthpiece in an open circuit either with or without a 10cmH<sub>2</sub>O resistive load. P<sub>0.1</sub> measurements were made on separate runs using the manual or computerised method in random order. Equipment dead space was 200ml. In the manual method the balloon was inflated every 20 seconds during expiration, and was deflated as soon as a positive pressure change was noted by the balloon operator. Mouth pressure was recorded onto a fast running 50mmsec chart recorder. P<sub>0.1</sub> was measured 100msec after the mouth pressure trace crossed zero. In the computerised method the balloon was inflated when expiration was sensed. P<sub>0.1</sub> was measured as the pressure 100msec after a 0.2cmH<sub>2</sub>O positive pressure swing had been detected by the computer. Balloon deflation occurred immediately after p<sub>0.1</sub> had been measured. Occlusions were repeated at similar intervals to the manual method.

In each subject inspiratory effort sensation (IES)(Borg Scale), p<sub>0.1</sub>, tidal volume, respiratory frequency and inspiratory and total cycle time were measured. Duty cycle, minute ventilation and mean inspiratory flow were derived.

During all runs music was played to the subjects to minimise environmental influences.

### Results

There were no differences between the breathing patterns during manual or computerised recordings either with or without the inspiratory resistive load. There were no significant differences between p<sub>0.1</sub> measurements by either method. The presence of the inspiratory resistive load increased

IES,  $p_{0.1}$ ,  $T_i$  and  $T_{tot}$ .  $ETCO_2$  and  $VE$  were unaltered whilst  $V_t/T_i$  fell (table A.5).

### Conclusion

The computerised method gives a reliable measure of occlusion pressure which compares closely with accepted manual techniques.

Table A.5

Computerised vs manual occlusion pressure measurement

|                                       | Manual      |            | Computer    |            |
|---------------------------------------|-------------|------------|-------------|------------|
|                                       | No Resistor | Resistor   | No resistor | Resistor   |
| IES                                   | 0.35(0.51)  | 1.22(1.2)  | 0.42(0.49)  | 1.39(1.24) |
| p0.1 (cmH <sub>2</sub> O)             | 1.89(0.59)  | 3.07(1.11) | 1.96(0.65)  | 3.03(1.03) |
| P <sub>ET</sub> CO <sub>2</sub> (kPa) | 4.62(0.19)  | 4.73(0.4)  | 4.6(0.28)   | 4.58(0.53) |
| VE (L)                                | 13(1.07)    | 12.4(1.20) | 13.1(0.9)   | 13.1(2.6)  |
| Ti (secs)                             | 1.39(0.26)  | 1.99(0.6)  | 1.45(0.42)  | 2.13(0.46) |
| Ttot (secs)                           | 3.68(0.69)  | 4.3(1.06)  | 3.78(0.73)  | 4.5(0.7)   |
| Vt/Ti                                 | 0.5(0.25)   | 0.46(0.08) | 0.59(0.12)  | 0.47(0.09) |

### Validation of mouth occlusion pressure in the presence of airflow limitation.

Mouth occlusion pressure was validated against oesophageal pressure which is not subject to the same pressure equilibration time constant artefact

### Methods

6 subjects with severe COPD were studied before and after 200 mcg oxitropium bromide during a CO<sub>2</sub> rebreathing experiment detailed earlier. Simultaneous measurements of mouth and oesophageal pressure were made from a chart recorder. Mouth occlusion pressure was taken as the pressure 100msec after a negative pressure swing had been detected. Oesophageal occlusion pressure was measured at 2 points, 100msec after a negative oesophageal pressure swing had been detected and also 100msec after a negative mouth pressure swing had been detected.

### Results

Oxitropium produced a range of bronchodilation, mean(SD) pre drug FEV<sub>1</sub> 0.8(0.32)L, post drug FEV<sub>1</sub> 0.95(0.43)L. Occlusion pressure was lower using mouth pressure than oesophageal pressure measured either way. The difference between mouth and oesophageal pressure both measured 100msec after a negative deflection occurred was greater before bronchodilator than after it. However the difference between mouth and oesophageal occlusion pressures measured at isotime was not affected by oxitropium bromide.

### Discussion

Mouth pressure was less than oesophageal pressure whichever way it was measured. The difference was more pronounced when the measurements were timed from different points rather than at isotime. The best method of timing oesophageal occlusion pressure is not certain. It should theoretically be measured 100msec from the beginning of a respiratory



effort to be comparable with the accepted method of measuring mouth occlusion pressure. The presence of significant degrees of PEEPi as in this group of patients makes this difficult to achieve in practice, furthermore the presence of auto PEEP implies that the respiratory system has not reached elastic recoil equilibrium and therefore the measurement of occlusion pressure may be invalid.

The administration of bronchodilator reduced the difference between mouth and oesophageal pressures timed from detection of a negative pressure swing. This suggests that shortening of the pressure equilibration time constants between alveolus and mouth occurred with bronchodilator. Thus bronchodilators cause mouth and oesophageal pressures to approach one another, mouth pressure will therefore rise artefactually to approach 'true' P0.1 which is theoretically better measured from oesophageal pressure in the presence of airflow obstruction. This finding may explain the absence of reductions in occlusion pressure following administration of bronchodilator despite significant falls in breathlessness.

The use of occlusion pressure measurement to measure changes in respiratory drive with changes in bronchial calibre in COPD is flawed.

Table A.6

Verification of occlusion pressure measurements in the presence of  
airflow obstruction

| (mean SD) pre medication |           |                   | post medication |           |                   |
|--------------------------|-----------|-------------------|-----------------|-----------|-------------------|
| mouth                    | oesoph    | isotime<br>oesoph | mouth           | oesoph    | isotime<br>oesoph |
| 6.5(5.1)                 | 8.5(4.5)* | 7.0(3.9)          | 6.6(5.1)        | 7.4(4.8)* | 7.4(3.8)**        |

\* different from mouth  $p < 0.001$ , \*\*  $p < 0.02$

## Oxitropium experiment

### Patient biographical details

|   | Sex | Age<br>Yrs | Smoking<br>history | Pack<br>yrs | FEV1 (L) | FEV1<br>% pred | Concurrent<br>medication    | Usual<br>b'dilators                                                      |
|---|-----|------------|--------------------|-------------|----------|----------------|-----------------------------|--------------------------------------------------------------------------|
| 1 | M   | 67         | Current            | 80          | 91       | 26             | Spironalactone<br>Frusemide | Salbutamol inh<br>Beclomethasone inh                                     |
| 2 | M   | 69         | Current            | 130         | M        | M              |                             | Salbutamol inh                                                           |
| 3 | F   | 68         | Non                | 0           | .6       | 28             |                             | Salbutamol inh<br>Ipratropium inh                                        |
| 4 | M   | 60         | Current            | 63          | 1.1      | 34             |                             | Salbutamol inh<br>Ipratropium inh<br>Beclomethasone inh                  |
| 5 | M   | 67         | Current            | 20          | 1.27     | 33             |                             | Salbutamol Inh                                                           |
| 6 | M   | 49         | Ex                 | 30          | .53      | 12             |                             | Salbutamol Inh<br>Ipratropium Inh                                        |
| 7 | M   | 49         | Ex                 | 10          | 1.04     | 36             | Ranitidine<br>Gastrocote    | Theophylline SR<br>Salbutamol inh                                        |
| 8 | M   | 67         | Ex                 | 20          | .88      | 25             |                             | Salbutamol inh<br>Beclomethasone inh                                     |
| 9 | M   | 62         | Ex                 | 50          | .94      | 33             |                             | Salbutamol inh<br>Beclomethasone inh<br>Theophylline SR<br>Salbutamol SR |

|    |   |    |         |    |      |    |                                    |                                                         |
|----|---|----|---------|----|------|----|------------------------------------|---------------------------------------------------------|
| 10 | M | 63 | Ex      | 80 | 1.06 | 34 |                                    | Duovent inh<br>Theophylline SR                          |
| 11 | M | 56 | Current | 25 | M    | M  |                                    | Salbutamol inh<br>Ipratropium inh<br>Theophylline SR    |
| 12 | M | 63 | Current | 60 | .58  | 18 | Cimetidine                         | Salbutamol inh<br>Theophylline SR                       |
| 13 | F | 66 | Ex      | 60 | .64  | 32 | Frusmide<br>Amiloride              | Duovent inh                                             |
| 14 | F | 70 | Ex      | 26 | .64  | 31 |                                    | Duovent inh<br>Beclomethasone inh<br>Theophylline SR    |
| 15 | M | 62 | Ex      | 75 | 1.05 | 34 |                                    | Salbutamol inh<br>Ipratropium inh<br>Beclomethasone inh |
| 16 | M | 49 | Ex      | 2  | 1.19 | 37 | Co codamol                         | Duovent inh<br>Beclomethasone inh<br>Theophylline SR    |
| 17 | M | 68 | Ex      | 22 | .83  | 37 | Isosorbide m'nitrate<br>Ranitidine | Duovent inh                                             |

|    |   |    |         |    |     |    |          |                                                                            |
|----|---|----|---------|----|-----|----|----------|----------------------------------------------------------------------------|
| 18 | M | 58 | Ex      | 30 | .69 | 21 | Digoxin  | Duovent inh<br>Beclomethasone inh                                          |
| 19 | M | 70 | Current | 30 | .86 | 24 |          | Salbutamol inh<br>Beclomethasone inh                                       |
| 20 | M | 58 | Ex      | 28 | .8  | 23 |          | Salbutamol inh<br>Beclomethasone inh                                       |
| 21 | M | 67 | Ex      | 55 | .57 | 25 |          | Duovent inh<br>Salbutamol neb                                              |
| 22 | M | 74 | Ex      | 12 | .58 | 22 |          | Salbutamol inh<br>Ipratropium inh<br>Beclomethasone inh<br>Salbutamol neb  |
| 23 | F | 67 | Current | 30 | .94 | 48 |          | Salbutamol inh<br>Ipratropium inh<br>Theophylline SR                       |
| 24 | F | 69 | Non     | 0  | .47 | 27 |          | Salbutamol inh<br>Ipratropium inh<br>Beclomethasone inh<br>Theophylline SR |
| 25 | F | 66 | Current | 45 | M   | M  |          | Salbutamol inh                                                             |
| 26 | F | 59 | Current | 30 | .38 | 16 | Premarin | Salbutamol inh                                                             |

|    |   |    |         |    |      |    |                        |                                                                            |
|----|---|----|---------|----|------|----|------------------------|----------------------------------------------------------------------------|
| 27 | F | 69 | Ex      | 15 | .44  | 19 |                        | Salbutamol inh<br>Ipratropium inh<br>Salbutamol neb                        |
| 28 | M | 66 | Ex      | 20 | .89  | 31 |                        | Salbutamol inh<br>Ipratropium inh<br>Theophylline SR                       |
| 29 | F | 47 | Current | 2  | 1.05 | 42 |                        | Salbutamol inh<br>Ipratropium Inh<br>Beclomethasone Inh                    |
| 30 | M | 55 | Ex      | 30 | .51  | 14 |                        | Salbutamol inh<br>Ipratropium inh<br>Theophylline SR                       |
| 31 | F | 71 | Ex      | 2  | .66  | 32 |                        | Duovent inh<br>Theophylline SR                                             |
| 32 | M | 62 | Non     | 0  | 1    | 26 |                        | Salbutamol inh<br>Beclomethasone inh                                       |
| 33 | F | 69 | Ex      | 32 | .51  | 23 | Frusemide<br>Amiloride | Salbutamol inh<br>Beclomethasone inh                                       |
| 34 | F | 72 | Ex      | 30 | .5   | 24 |                        | Salbutamol inh<br>Ipratropium inh<br>Theophylline SR                       |
| 35 | F | 54 | Ex      | 1  | .66  | 32 | Ranitidine             | Salbutamol inh<br>Ipratropium inh<br>Beclomethasone inh<br>Theophylline SR |

## REFERENCES

- Adams L, Chronos N, Lane R, Guz A: The measurement of breathlessness induced in normal subjects- validity of 2 scaling techniques. *Clin Sci* 1985;69:7-16
- Agnew JE, Pavia D, Clark SW: Airways penetration of inhaled radioaerosol; an index to small airway function? *Eur J respir Dis* 1981;62:239-255
- Aldrich TK, Arora NS, Rochester DF: The influence of airway obstruction and respiratory muscle strength on maximal voluntary ventilation in lung disease. *Am Rev Respir Dis* 1982;126:195-199
- Allen MB, Pugh J, Wilson RSE: Nebuhaler or nebuliser for high dose bronchodilator therapy in chronic bronchitis. *Br J Dis Chest* 1988;82:368-373
- Altose MD, Kelsen SG, Stanley NN, Levinson RS, Cherniak NS, Fishman AP: Effect of hypercapnia on occlusion pressure in conscious man. *J Appl Physiol* 1976;40:338-344
- Altose MD: Assessment and management of breathlessness. *Chest* 1985;88:77S-81S
- Arora NS, Rochester DF: Effect of body weight and muscularity on human diaphragm muscle mass, thickness and area. *J Appl Physiol* 1982;52:64-70
- Barach AL: The therapeutic use of helium. *J A M A* 1936;107:1273-1280
- Barbera JA, Ramirez J, Roca J, Wagner PD, Sanchez-Lloret J, Rodriguez-Roisin R: Lung structure and gas exchange in mild chronic obstructive pulmonary disease. *Am Rev respir Dis* 1990;141:895-901
- Barnes PJ: Cholinergic control of airway smooth muscle. *Am Rev Respir Dis* 1987;136:s42-s45
- Bayliss CE, Robertson GW: The visco elastic properties of the lungs. *Q J Exper Physiol* 1939;29:27
- Bedell GN, Marshall R, DuBois AB, Comroe JH: Plethysmographic determination of gas trapped in the lungs. *J Clin Invest* 1956;35:664-670
- Begin P, Peslin R: Influence of panting frequency on TGV measurements in COPD. *Am Rev Respir Dis* 1984;130:121-123
- Bel EH, Zwinderman AH, Timmers MC, Dijkman JH, Sterk RJ: the protective effect of a beta agonist against excessive airway narrowing in response to bronchoconstrictor stimuli in asthma and chronic obstructive lung disease. *Thorax* 1991;46:9-14
- Bellemare F, Grassino A: Effect of pressure and timing of contraction on human diaphragm fatigue. *J Appl Physiol* 1982;53:1190-1195

- Bellemare F, Grassino A: Evaluation of human diaphragm fatigue. *J Appl Physiol* 1982;53:1196-1206
- Bellemare F, Grassino A: Force reserve of the diaphragm in patients with chronic obstructive pulmonary disease. *J Appl Physiol* 1983;55:8-15
- Bellamy D, Hutchison DCS: The effects of salbutamol aerosol on lung function in patients with pulmonary emphysema. *Br J Dis Chest* 1981;75:190-196
- Berend N, Wright JL, Thurlbeck WM et al Small airways disease reproducibility of measurement and correlation with lung function. *Chest* 1981;79:263-268
- Berger R, Smith D (1): Effect of inhaled metaproterenol on exercise performance in patients with stable fixed airway obstruction. *Am Rev Respir Dis* 1988;138:624-629
- Berger R, Smith D (2): Acute postbronchodilator changes in pulmonary function parameters in patients with chronic airways obstruction. *Chest* 1988;93:541-546
- Bernhard HJ, Pierce JA, Joyce JW, Bates JH: Roentgenographic determination of TLC. A new method evaluated in health, emphysema and congestive cardiac failure. *Am J Med* 1960;28:51-60
- Blackie SP, Al-Majed S, Staples CA, Hilliam C, Pare PD: Changes in total lung capacity during acute spontaneous asthma. *Am Rev Respir Dis* 1990;142:79-83
- Bland JM, Altman DG: statistical methods for assessing agreement between 2 methods of clinical measurement. *Lancet* 1986;1:307-310
- Bohadana AB, Peslin R, Hannhart B, Teculescu D: Influence of panting frequency on plethysmographic measurements of thoracic gas volume. *J Appl Physiol* 1982;52:739-747
- Borg G: Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2-3:92-98
- Borg GAV: psychophysical basis of perceived exertion. *Med Sci Sports Med* 1982;14:377-381
- Bradly BL, Forman JW, Miller WC: Low density gas breathing during exercise in chronic obstructive lung disease. *Respiration* 1980;40:311-316
- Briscoe WA, DuBois AB: The relationship between airway resistance, airway conductance and lung volume in subjects of differing age and body size. *J Clin Invest* 1958;37:1279-1285
- Britton J, Hanley SP, Garrett HV, Hadfield JW, Tattersfield AE: Dose related effects of salbutamol and ipratropium bromide on airway calibre and reactivity in subjects with asthma. *Thorax* 1988;63:300-305



Brown R, Ingram RH, McFadden ER: Problems in the plethysmographic assessment of changes in total lung capacity in asthma. *Am Rev Respir Dis* 1978;118:685-692

Brown R, Hoppin FG, Ingram RH, Saunders NA, McFadden ER: Influence of abdominal gas on the Boyles Law determination of thoracic gas volume. *J Appl Physiol* 1978;44:469-473

Brown R, Scharf S, Ingram RH: Non homogenous alveolar pressure swings in the presence of airway closure. *J Appl Physiol* 1980;49:398-402

Brown R, Slutsky AS: Frequency dependence of plethysmographic measurement of thoracic gas volume. *J Appl Physiol* 1984;57:1865-1871

Brown SE, Prager RS, Shinto RA, Fisher CE, Stansbury DW, Light RW: cardiopulmonary responses to exercise in chronic airflow obstruction: effects of atropine sulfate. *Chest* 1986;89:7-11

Burki NK: The effect of changes in functional residual capacity with posture on occlusion pressure and ventilatory pattern. *Am Rev Respir Dis* 1977;116:895-900

Burki NK: Breathlessness and mouth occlusion pressure in patients with chronic obstruction of the airways. *Chest* 1979;76:527-531

Burns BH, Howell JBL: Disproportionately severe breathlessness in chronic bronchitis. *Q J Med* 1969;38:277-294

Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM: Two, six and twelve minute walking tests in respiratory disease. *Br Med J* 1982;284:1607-1608

Bye PTB, Esau SA, Levy RD: Ventilatory function during exercise in air and oxygen in patients with chronic airflow limitation. *Am Rev Respir Dis* 1985;132:236-240

Calverley PMA: The clinical efficacy of oxitropium bromide. Contemporary reviews of pharmacotherapy 1992 (In press)

Campbell EJM, Guz A: Breathlessness. in *Lung Biology in Health and Disease* New York, Dekker 1981: 1181-1195

Campbell EJM, Howell JBC: The Sensation of Breathlessness. *Brit Med Bull* 1963;19:36-40

Campbell EJM, Freedman S, Clark TJH, Robson JG, Norman J The effect of muscular paralysis induced by tubocurarine on the duration and sensation of breathholding. *Clin Sci* 1967;32:425-432

Campbell EJM, Godfrey S, Clark TJH, Freedman S, Norman J. The effect of muscular paralysis with tubocurarine on the duration and sensation of breathholding during hypercapnia *Clin Sci* 1969;36:323-328

Campbell JA, Hughes RL, Sahgal V et al: Alterations in intercostal muscle morphology and biochemistry in patients with chronic obstructive lung disease. *Am Rev Respir Dis* 1980;122:679-686

- Capel LH, Smart J: Obstructive airway disease- measurements of effort intolerance and forced expiratory volume in bronchitis, emphysema and asthma. *Lancet* 1959(May):960-962
- Chai H, Farr RS, Froehlich LA et al: Standardisation of bronchial inhalation challenge procedures. *J Allergy Clin Immunol* 1975;56:323-7
- Chonan T, Altose MD, Cherniak NS: Effects of expiratory resistive loading on the sensation of dyspnoea. *J Appl Physiol* 1990;69:91-95
- Chrystyn H, Mulley BA, Peake MD: Dose response relation to oral theophylline in severe COPD *Br Med J* 1988;287:1506-1510
- Chung KF, Snashall PD: Effect of prior bronchoconstriction on the airway response to histamine in normal subjects. *Thorax* 1984; 40-45
- Ciba Guest Symposium: Terminology, definitions and classifications of chronic pulmonary emphysema and related conditions. *Thorax* 1959;14:286-99.
- Citterio G, Agostoni E, Del Santo A, Marazzini L: Decay of inspiratory muscle activity in chronic airway obstruction *J Appl Physiol* 1981;51:1388-1397
- Clague JE, Carter J, Pearson MG and Calverley PMA: Effort sensation, chemoreceptors and breathing pattern during inspiratory resistive loading. *J Appl Physiol* 1992;73:440-445
- Clausen JL: In Clausen JL ed. *Pulmonary function testing Guidelines and Controversies*. New York:1982, Grune and Stratton:141-153
- Clements JA, Sharp JT, Johnson RP, Elam JO: Estimation of pulmonary resistance by repetitiv interruption of airflow. *J Clin Invest* 1959;38:1262-1270
- Connellan SJ, Gough SE: The effects of nebulised salbutamol on lung function and exercise tolerance in patients with severe airflow obstruction. *Br J Dis Chest* 1982;76:135-142
- Cooper KH: A means of assessing maximal oxygen uptake. Correlation between field and treadmill testing. *JAMA* 1968;203:135-138
- Corris PA, Neville E, Nariman S, Gibson GJ: Dose response study of inhaled salbutamol powder in chronic airflow obstruction. *Thorax* 1983;38:292-296
- Cosio MG, ghezzi H, Hogg JC et al: The relations between structural changes in small airways and pulmonary function tests. *N Engl J Med* 1978;298:1277-1281
- Criner G.J. Cell BR: Ventilatory muscle recruitment in exercise with O<sub>2</sub> in obstructed patients with mild hypoxaemia *J Appl Physiol* 1987;63:195-200
- Crompton GK: A comparison of responses to bronchodilator drugs in chronic bronchitis and emphysema. *Thorax* 1968;23:46-55
- Cropp A, Zuti R, Kendis C, Altose MD: Determinants of the sensation of breathlessness in patients with COPD. *Am Rev Respir Dis* 1984;129:A240

Cropp A, Dimaro AF: Effects of intermittent negative pressure ventilation on respiratory muscle function in patients with severe COPD Am Rev Respir Dis 1987;135:1056-1061

Davidson AC, Leach R, George RJD, Geddes DM: Supplemental oxygen and exercise ability in chronic obstructive airways disease. Thorax 1988;43:965-971

Davis C, Kannan MS, Jones TR, Danial EE: control of human airway smooth muscle in in vitro studies. J Appl Physiol 1982;53:1080-1087

Dejours P, Rahn H: Residual volume measurement by the methods of helium substitution and volume expansion. J Appl Physiol 1953;5:445

Desmond KJ, Demizio DL, Allen PD, Beaudry PH, Coates AL: An alternate method for the determination of functional residual capacity in a plethysmograph. Am Rev Respir Dis 1988;137:273-276

Ding DJ, Martin JG, Macklem PT: Effects of lung volume on maximal methacholine induced bronchoconstriction in normal humans. J Appl Physiol 1987;62:1324-1330

Dodd DS, Brancatisano T, Engel LA, Chest wall mechanics during exercise in patients with severe chronic airflow limitation Am Rev Respir Dis 1984;129:33-38

Douglas NJ, Davidson I, Sudlow MF, Flenley DC: Bronchodilatation and the site of airway resistance in severe chronic bronchitis. Thorax 1979;34:51-56

DuBois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH: A rapid plethysmographic method for measuring thoracic gas volume: A comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. J Clin Invest 1956;35:322-326

DuBois AB, Botelho SY, Comroe JH: A new method for measuring airways resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory diseases. J Clin Invest 1956;35:327-335

DuBois AB, Brody AW, Lewis DH, Burgess BF: Oscillation mechanics of the lung and chest in man. J Appl Physiol 1956;8:587-594

Dutoit JI, Woolcock AJ, Salome CM, Sundrum R, Black JL: Characteristics of bronchial hyperresponsiveness in smokers with chronic airflow limitation. Am Rev Respir Dis 1986;134:498-501

Edwards RHT Human muscle function and fatigue. In Human Muscle fatigue: Physiological mechanisms. London, Pittman Medical (Ciba Symposium 82) 1981, p1-18

Eldridge F, Vaughn KZ: Relationship of thoracic volume and airway occlusion pressure, muscular effects. J Appl Physiol 1971;31:535-543

Elliott MW, Adams L, Cockcroft A, Macrae KD, Murphy K, Guz A: The language of breathlessness. Use of verbal descriptors by patients with cardiopulmonary disease. Am Rev Respir Dis 1991;144:826-832

- El Manshawi, Killian KJ, Summers E, Jones NL: Breathlessness during exercise with and without resistive loading J Appl Physiol 1986;61:896-905
- Evanlich MJ, Lopata M, Lourenco RV: Phrenic nerve activity and occlusion pressure changes during CO<sub>2</sub> rebreathing in cats. J Appl Physiol 1976;41:536-543
- Farkas GA, Rousos C: Adaptability of the hamster diaphragm to exercise and or emphysema J Appl Physiol 1983;53:1263-1272
- Farkas GA, Rousos C: Diaphragm in emphysematous hamsters: sarcomere adaptability. J Appl Physiol 1983;54:1635-1640
- Felsen B Chest Roentgenology Saunders, Philadelphia 1973
- Fletcher CM, Pride NB: Definitions of emphysema, chronic bronchitis, asthma and airflow obstruction 25 years on from the CIBA symposium. Thorax 1984;39:81-85
- Fowler WS: Breaking point of breath holding. J Appl Physiol 1954;6:539-545
- Freedman BJ, The functional geometry of the bronchi Bull Physiopathol Respir 1972;8:545-551
- Frith PA, Jenner B, Atkinson J: Effects of inhaled oxitropium bromide and fenoterol alone and in combination in chronic airflow obstruction. Respiration 1986;50:294-297 (suppl 2) (1)
- Frith PA, Jenner B, Dangerfield R, Atkinson J, Drennan C: Oxitropium bromide a novel anticholinergic drug: A dose response and time response study. Chest 1986;89:249-253 (2)
- Fry DL, Ebert RV, Stead WW, Brown CC: The mechanisms of pulmonary ventilation in normal subjects and in patients with emphysema. Am J Med 1954;16:80
- Gilbert R, Keighley J, Auchinloss JA: Disability in patients with obstructive pulmonary disease. Am Rev Respir Dis 1964;90:283-294
- Gorini M, Spinelli A, Ginanni R, Duranti R, Giglioti F, Arcangeli p Scano G: Neural respiratory drive and neuromuscular coupling during CO<sub>2</sub> rebreathing in patients with chronic interstitial lung disease. Chest 1989;96:824-830
- Gottfried SB, Altose MD, Kelsen SG, Fogarty CM, Cherniak NS: The perception of changes in airflow resistance in normal subjects and in patients with chronic airways obstruction. chest 1978;73:286-288
- Gottfried SB, Redline S, Altose MD: Respiratory sensation in COPD. Am Rev Respir Dis 1985;132:954-959
- Grape B, Channin E, Tyler JM: the effect of helium and oxygen mixtures on pulmonary resistance in emphysema. Am Rev Respir Dis 1960;81:823-829

Grassinio AE, Derenne JP, Almirall J, Milic Emili J, Whitelaw W: Configuration of the chest wall and occlusion pressure in awake humans. *J Appl Physiol* 1981;50:134-142

Greenspon LW, Parrish B: Inhibition of methacholine induced bronchoconstriction in patients with COPD. *Am Rev Respir Dis* 1988;137:281-285

Gribben HR, Gardiner IT, Heinz GJ, Gibson GJ, Pride NB: Role of impaired muscle function in limiting the ventilatory response to carbon dioxide in chronic airflow obstruction. *Clin Sci* 1983;64:487-495

Grimby G, Elgefors B, Oxhoj H: ventilatory levels and chest wall mechanics during exercise in obstructive lung disease. *Scand J Respir Dis* 1973;54:45-52

Grimby G, Stiksa J: Flow volume curves and breathing patterns during exercise in patients with obstructive lung disease *Scand J clin Lab Invest* 1970;25:303-313

Gross NJ, Bankwala Z: Effects of an anticholinergic bronchodilator on arterial blood gases of hypoxaemic patients with COPD. Comparison with a B adrenergic agent. *Am Rev Respir Dis* 1987;136:1091-1094

Gross NJ, Skorodin MS: Role of parasympathetic system in airway obstruction due to emphysema. *N Engl J Med* 1984;311:421-5

Grunstein MM, Younes m, Milic Emili J: Control of tidal volume and respiratory frequency in anaesthetised cats. *J Appl Physiol* 1973;35:463-476

Gunawardena KA, Smith AP, Shankleman J: A comparison of metered dose inhalers with nebulisers for the delivery of ipratropium in domicillary practice. *Br J Dis Chest* 1986;80:170-178

Gutierrez M, Beroiza T, Contreras G, Diaz O, Cruz E, Moreno R, Lisboa C: Weekly cuirass ventilation improves blood gases and inspiratory muscle strength in patients with chronic airflow limitation and hypercarbia. *Am Rev Respir Dis* 1988;138:617-623

Guyatt AR, Alpers JH: Factors affecting airways conductance: a study of 752 working men. *J Appl Physiol* 1968;24:310-316

Guyhatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman lb, Jones NL, Fallen EC, Taylor DW: Effect of encouragement on walking test performance. *Thorax* 1984;39:818-822

Guyhatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW: A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773-778

Haddad H, Engel LA: Influence of panting technique on the plethysmographic measurement of thoracic gas volume. *Am Rev Respir Dis* 1978;117:265-271

Hale KA, Ewing SL, Gosnell BA, Neiwohner DE: Lung disease in long term cigarette smokers with and without chronic airflow limitation *Am Rev Respir Dis* 1984;130:716-721

Haluska J, Chartrand DA, Grassino AE, Milic-Emili J: Intrinsic PEEP and Arterial PCO<sub>2</sub> in stable patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990;141:1194-1197

- Harris TR, Pratt PC, Kilburn KH: Total lung capacity measured by roentgenograms. *Am J Med* 1971;50:756-763
- Hay JG, Carter J, Pearson MG, Calverley PMA: Oxygen desaturation and breathlessness during exercise in COPD *Am Rev Respir Dis* 1990:A552 (Abstract)
- Higgenbottom T, Payne J: Glottis narrowing in lung disease *Am Rev Respir Dis* 1982;125:746-750
- Higgins BG, Powell RM, Cooper S, Tattersfield AE: Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. *Eur Respir J* 1991(4);418-420
- Hill C, Flack M: The effect of excess carbon dioxide and of want for oxygen upon the respiration and the circulation. *Journal of Physiology* 1908;37:77-111
- Hitchcock FA, Edelman A, Shelden FF, Whitehorn MV: The volume and composition of air expelled from the lungs during explosive decompression *Fed Proc* 1946;5:48
- Howell JBC Breathlessness in pulmonary disease. In *Breathlessness*: eds JBC Howell and EJM Campbell 1966: Davis Philadelphia 167-177
- Hudgel DW, Cooperson DM, Kinsman RA: Recognition of added resistive loads in asthma. *Am Rev Respir Dis* 1982;126:121-25
- Hugh-Jones P, Lambert AV: A simple standard exercise test and its use for measuring exertional dyspnoea *Br Med J* 1952;1:65-71
- Hurtado A, Fray WH: Studies of total lung capacity and its subdivisions. Correlation with physical and radiological measurements *J Clin Invest* 1933;12:807-823
- Hyatt RE: Expiratory flow limitation. *J Appl Physiol* 1983;55:1-8
- Hyatt RE, Flath RE: Relationship of airflow to pressure during maximal respiratory effort in man. *J Appl Physiol* 1966;21:477-482
- Ishikawa S, Hayes JA: Functional morphometry of the diaphragm in patients with chronic obstructive lung disease. *Am Rev Respir Dis* 1973;108:135-138
- Jaeger M: Effect of the cheeks and the compliance of alveolar gas on the measurement of respiratory variables. *Respiration Physiology* 1982;47:325-340
- Jardim J, Farkas G, Prefaut C et al : The failing respiratory muscles under normoxic and hypoxic conditions *Am Rev Respir Dis* 1981;124:274-279
- Jenkins SC, Heaton RW, Fulton TJ, Moxham J: Comparison of domiciliary nebulised salbutamol and salbutamol from a metered dose inhaler in stable airflow limitation. *Chest* 1987;91:804-807
- Jenkins SC, Moxham J: High dose salbutamol in chronic bronchitis, comparison of 400mcg, 1mg, 1.6mg, 2mg and placebo delivered by rotahaler. *Br J Dis Chest* 1987;81:242-247

- Jones NL, Jones G, Edwards RHT: Exercise tolerance in chronic airway obstruction. *Am Rev Respir Dis* 1971;103:477-491
- Jones NL, Kearon MC, LeBlanc P, Martin D, Campbell EJM, Killian KJ: Symptoms limiting activity in chronic airflow limitation. *Am Rev Respir Dis* 1989;139:A319 (abstract)
- Jones RW, Wakefield JM, Kontaki E: A simple and portable paced step test for reproducible measurements of ventilation and oxygen consumption during exercise. *Thorax* 1987;42:136-143
- Juan G, Calverley P, Talamo C et al: Effect of carbon dioxide on diaphragmatic function in human beings. *N Engl J Med* 1984;310:874-879
- Karpel JP: Bronchodilator responses to anticholinergic and  $\beta$  adrenergic agents in stable COPD *Chest* 1991;99:871-876
- Katch FI: Optimal duration of endurance performance on the cycle ergometer in relation to maximal oxygen uptake. *Ergonomics* 1973;203:227-235
- KAwakami Y, Yamamoto H, Yoshikawa T, Shida A: Chemical and behavioural control of breathing in twin adults. *Am Rev Respir Dis* 1984;129:703-707
- Keens TG, Kratins IRB, Wannamaker EM: Ventilatory muscle endurance training in normal subjects and patients with cystic fibrosis. *Am Rev Respir Dis* 1977;116:853-860
- Kelsen SG, Fleeger B, Altose MD: The respiratory neuromuscular response to hypoxia, hypercapnia and obstruction to airflow in asthma. *Am Rev Respir Dis* 1979;120:517-527
- Kelsen SG, Prestel TF, Cherniak NS, Chester EH, Deal EC: Comparison of the respiratory responses to external resistive loading and bronchoconstriction. *J Clin Invest* 1981;67:1761-1768
- Kelsen SG, Wolanski T, Supinski GS, Roessman V: The effect of elastase induced emphysema on diaphragmatic muscle structure in hamsters. *Am Rev Respir Dis* 1983;127:330-334
- Kilburn KH, Warshaw RH: Airway obstruction in asbestosis exposed shipyard workers with and without irregular opacities. *Respir Med* 1990;84:449-455
- Killian KJ: Dyspnoea and exercise *Ann Rev Physiol* 1983;45:465-79
- Killian KJ, Gandevia SC, Summers E, Campbell EJM: Effect of increased lung volume on perception of breathlessness effort and tension. *J Appl Physiol* 1984;57:686-691
- King B, Coates JE: Relation of lung function and exercise capability to mood and attitudes to health. *Thorax* 1989;44:402-409
- Knox AJ, Morrison JFJ, Muers MF: Reproducibility of walking tests results in chronic obstructive airways disease. *Thorax* 1988;43:388-392
- Knudson RJ, Slatin RC, Lebowitz MD, Burrows B: The maximum expiratory flow volume curve: normal standards- variability with age. *Am Rev Respir Dis* 1976;113:587-600

- Macklem PT, Macklem DM, DeTroyer A: A model of inspiratory muscle mechanics. *J Appl Physiol* 1983;55:547-557
- Mahler DA, Mattley RA, Snyder PE, Wells CK, Loke J: Sustained release theophylline reduces dyspnoea in nonreversible obstructive airway disease *Am Rev Respir Dis* 1985;131:22-25
- Manning HL, Basner R, Ringler J, Rand C, Fencel V, Weinberger S, Schwarzstein RM: The effect of chest wall vibration on the perception of breathlessness *J Appl Physiol* 1991;71:175-181
- Marazzini L, Casestri R, Gori D, Gatti L, Longhini E: Difference between mouth and esophageal occlusion pressure during CO<sub>2</sub> rebreathing in COPD. *Am rev Respir Dis* 1978;118:1027-1033
- Martin JG in: Roussos C, Macklem P, eds *The Thorax*. New York:1985, Marcell Dekker 899-921
- McFadden ER, Kiser R, DeGroot WJ: Acute bronchial asthma, relation between clinical and physiological manifestations *N Engl J Med* 1973;288:221-225
- McGavin CR, Artvinli M, Naoe H, McHardy GJR: Dyspnoea, disability and distance walked: comparison of estimates of exercise performance in respiratory disease. *Br Med J* 1978;2:241-243
- McGavin CR, Gupta SP, McHardy GJR: Twelve minute walking test for assessing disability in chronic bronchitis. *Br Med J* 1976;1:822-823
- McGavin CR, Gupta SP, Lloyd EL, McHardy GJR: Physical rehabilitation for the chronic bronchitic: Results of a controlled trial of exercises in the home. *Thorax* 1977;32:307-311
- McGavin CR, Naoe H, McHardy GJR: Does inhalation of salbutamol enable patients with airway obstruction to walk further? *Clin Sci* 1976;51:129
- McIlroy MB, Christie RV: The work of breathing in emphysema. *Clin Sci* 1954;13:147-154
- McIlroy MB, Mead J, Selverstone NJ, Radford EP: Measurement of lung tissue viscous resistance using gases of equal kinematic viscosity *J Appl Physiol* 1955;7:485
- McKensie HI, Glick M, Outhred KG: Chronic bronchitis in coal miners: Ante mortem/post mortem comparisons. *Thorax* 1969;24:527-535
- McMichael J: A rapid method of determining lung capacity *Clin Sci* 1939;4:167-173
- Mead J: Volume displacement body plethysmograph for respiratory measurements in human subjects. *J Appl Physiol* 1960;15:736
- Mead J, Whittenberger JL: Evaluation of airway interruption technique as a method of measuring pulmonary airflow resistance. *J Appl Physiol* 1954;6:408
- Medical Research Council: Standardised questionnaire on respiratory symptoms. *Br Med J* 1960;2:1665-1668



- Medical Research Council: Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet* 1965;i:775-9
- Meisel JC, Silvers GW, Mitchell RS, Petty TL: Bronchial atrophy and dynamic expiratory collapse. *Am Rev Respir Dis* 1968;98:988-997
- Milic Emili J, Zin WA: Relationship between neuromuscular drive and ventilatory output. In *Handbook of Physiology. The Respiratory System*. Bethesda MD. American Physiological Society 1986 Section 3 Chapter 35 p631-646
- Millman RP, Silage DA, Peterson DD, Pack AI: Effect of aerosolised histamine on occlusion pressure and ventilation in humans. *J Appl Physiol* 1982;53:690-697
- Minh VD, Lee HM, Dolan GF, Light RW, Bell J, Vasquez P: Hypoxaemia during exercise in patients with COPD. *Am Rev Respir Dis* 1979;120:787-794
- Mitchell DM, Gildeh P, Rehahn M, Dimond AH, Collins JV: Effects of oral prednisolone in chronic airflow obstruction. *Lancet* 1984;1:193-196
- Moreno RH, Hogg JC Pare PD: Mechanics of Airway Narrowing. *Am Rev Respir Dis* 1986;133:1171-1180
- Morgan AD, Peck DF, Buchanan DR, McHardy GJR: Effect of attitudes and beliefs on exercise tolerance in chronic bronchitis. *Br Med J* 1983;286:171-173
- Morice A, Smithies T: The 100m walk: a simple and reproducible exercise test. *Br J Dis Chest* 1984;78:392-394
- Morris MJ, Madgewick RG, Frew AJ Lane DJ: Breathing muscle activity during expiration in patients with chronic airflow obstruction. *Eur Respir J* 1990(3);901-909
- Mueller RE, Petty TL, Filley GF: Ventilation and arterial blood gas changes induced by pursed lips breathing. *J Appl Physiol* 1970;28:784-789
- Mullen JBM, Wiggs BR, Wright JL, et al: Reassessment of inflammation of the airways in chronic bronchitis *Br Med J* 1985;291:1235-1239
- Mungall IPF, Hainsworth R: Assessment of respiratory function in patients with COAD. *Thorax* 1979;34:254-258
- Murciano D, Aubier M, Bussi S, Derenne J-P, Pariente R, Milic-Emili J: Comparison of oesophageal, tracheal, and mouth occlusion pressure in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis* 1982;126:8376-841.
- Muza SR, Silverman MT, Gilmore GC, Hellerstein HK, Kelsen SG: Comparison of scales used to quantitate the sense of effort to breath in patients with COPD. *Am Rev Respir Dis* 1990;141:909-913
- Nagai A, West WW, Thurlbeck WM: The National Institutes of Health IPPB Trial: Pathology Studies. ii) Correlation between morphologic findings,

clinical findings and evidence of expiratory flow limitation. *Am Rev Respir Dis* 1985;132:916-953

Nisar M, Walshaw M, Earis JE, Pearson MG, Calverley PMA: Assessment of reversibility of airways obstruction in patients with chronic obstructive airways disease. *Thorax* 1990;45:190-194

O'Donnell DE, Sanii R, Anthonisen NR, Younes M: Effect of dynamic airway compression on breathing pattern and respiratory sensation in severe COPD. *Am Rev Respir Dis* 1987;135:912-918

O'Donnell DE, Sanii R, Giesbrecht G, Younes M: Effect of continuous positive airway pressure on respiratory sensation in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988;138:1185-1191

O'Driscoll BRC, Kay RJ, Bernstein A: Home nebulisers: can optimal therapy be predicted by laboratory studies. *Respir Med* 1990;84:471-477

O'Reilly JF, Shaylor JM, Fromings KM, Harrison BDW: The use of the 12 minute walking test in assessing the effect of oral steroid therapy in patients with chronic airways obstruction.

Olafsson S Hyatt RE: Ventilatory mechanics and expiratory flow limitation during exercise in normal subjects *J Clin Invest* 1969;48:564-573

Olivén A, Cherniak NS, Deal EC, Kelsen SG: The effects of acute bronchoconstriction on respiratory activity in patients with COPD. *Am Rev Respir Dis* 1985;131:236-241

Orehek J, Gayraud P, Smith AP, Grimoud C, Charpin J: Airway response to carbachol in normal and asthmatic subjects- distinction between bronchial sensitivity and reactivity. *Am Rev Respir Dis* 1977;115:937-943

Owens GR, Rogers RM, Pennock BE, Levin d: The diffusing capacity as a predictor of arterial oxygen desaturation during exercise in patients with COPD. *N Eng J Med* 1984;310:1218-1221

Pardy RL, Rivington RN, Despas PJ, Macklem PT: The effect of inspiratory muscle training on exercise performance in chronic airflow limitation. *Am Rev Respir Dis* 1981;123:426-433

Papiris S, Galavotti V, Sturani C: Effects of Beta agonists on breathlessness and exercise tolerance in COPD. *Respiration* 1986;49:101-108

Pardy RL, Rivington RN, Milic-Emili J, Mortola JP: Control of breathing in COPD- the effect of histamine inhalation. *Am Rev Respir Dis* 1982;125:6-11

Pare PD, Wiggs BJR, Coppin CA: Errors in the measurement of total lung capacity in chronic obstructive lung disease. *Thorax* 1983;38:468-471

Pare PD, Wiggs BR, James A, Hogg JC, Bosken C: The comparative mechanics and morphology of airways in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;143:1189-1193.

- Peacock A, Busst C, Dawkins K, Denison DM: Response of pulmonary circulation to oral pirbuterol in chronic airflow limitation. *Br Med J* 1983;287:1178-1180
- Peel ET, Anderson G,: Dose response study of oxitropium bromide in chronic bronchitis. *Thorax* 1984;39:453-456 (1)
- Peel ET, Anderson G, Cheong B, Broderick N: A comparison of oxitropium bromide and ipratropium bromide in asthma. *Eur J Respir Dis* 1984;65:106-108
- Pepe PE, Marini JJ: Occult PEEP in mechanically ventilated patients with airflow obstruction. *Am Rev Respir Dis* 1982;126:166-170
- Peslin R, Relationship between esophageal and alveolar pressure variations during occlusion. *J Appl Physiol* 1983;1172-1173 (letter)
- Petrof BJ, Calderini E, Gottfried SB: Effect of CPAP on respiratory effort and dyspnoea during exercise in severe COPD. *J Appl Physiol* 1990;69:179-188
- Petrof BJ, Legare M, Goldberg P, Milic-Emili J, Gottfried SB: Continuous positive airway pressure reduces work of breathing and dyspnoea during weaning from mechanical ventilation in severe COPD. *Am Rev Respir Dis* 1990;141:281-289
- Petty TL, Silvers GW, Stanford RE: Small airway dimension and size distribution in human beings with an increased closing capacity. *Am Rev Respir Dis* 1982;125:535-539
- Petty TL, Silvers GW, Stanford RE: Radial traction and small airway disease in excised human lungs. *Am Rev Respir Dis* 1986;133:132-135
- Pierce RJ, Brown DJ, Holmes M, Cumming G, Denison DM: Estimation of lung volumes from chest radiographs using shape information. *Thorax* 1979;34:726-734
- Postma DS, De Vries K, Koeter GH, Sluiter HJ: Independent influence of reversibility of airflow obstruction and non specific hyperreactivity in the long term course of lung function in chronic airflow obstruction. *Am Rev Respir Dis* 1986;134:276-280
- Potter WA, Olafsson S, Hyatt RE: Ventilatory mechanics and expiratory flow limitation during exercise in patients with obstructive lung disease. *J Clin Invest* 1971;51:910-918
- Pratt PC, Klugh GA: A method for the determination of total lung capacity from posteroanterior and lateral chest roentgenograms. *Am Rev Respir Dis* 1967;96:548
- Ramsdale EH, Morris MM, Roberts RS, Hargreave FE: Bronchial responsiveness to methacholine in chronic bronchitis, relationship to airflow obstruction and cold air responsiveness. *Thorax* 1984;39:912-918
- Rebuck AJ and Slutsky: Control of breathing in diseases of the respiratory tract and lungs. In *Handbook of Physiology. The respiratory system. Control of breathing*. Bethesda MD American Physiological Society 1986, section 3, volume 2, chapter 2, p771-791

- Rigg JRA, Rebuck AS, Campbell EJM: A study of the factors influencing relief of discomfort in breathing in normal subjects. Clin Sci Mol Med 1974;47:193-199
- Rochester DF, Braun NMT: Determinants of maximal expiratory pressure in chronic obstructive pulmonary disease. Am Rev respir Dis 1985;132:42-47
- Rochester DF, Braun NMT, Arora NS: Respiratory muscle strength in chronic obstructive pulmonary disease 1979;119:151-154
- Rodenstein DO, Francis C, Stanescu DC: Airway closure in humans does not result in overestimates of plethysmographic lung volume. J Appl Physiol 1983;55:1784-1989
- Rodenstein DO, Stanescu DC: Frequency dependence of plethysmographic volume in healthy and asthmatic subjects. J Appl Physiol 1983;54:159-163
- Rodenstein DO, Stanescu DC, Francis C: Demonstration of failure of body plethysmography in airway obstruction. J Appl Physiol 1982;52:949-954
- Roussos C, Macklem PT: The respiratory muscles. N Engl J Med 1982;307:786-797
- Rothstein MS, Zelefsky MN, Eichacker PQ, Rudolph DJ, Williams HM: Radiographic measurement of total lung capacity in acute asthma: Thorax 1989;44:510-512
- Saetta M, Ghezzi H, Kim WD, et al: Loss of alveolar attachments in smokers. A morphological correlate of lung function impairment. Am Rev Respir Dis 1985;132:894-900
- Salmon RB, Saidel GM, Inkley SR, Neiwoehner DE: Relationship of ventilation inhomogeneity to morphologic variables in excised human lungs. Am Rev Respir Dis 1982;126:686-690
- Schwarzstein RM, Lahivek K, Pope A, Weinberger SE, Weiss JW: Cold facial stimulation reduces breathlessness induced in normal subjects. Am Rev Respir Dis 1987;136:58-61
- Schwarzstein RM, Simon PM, Weiss JW, Fencel V, Weinberger SE: Breathlessness induced by dissociation between ventilation and chemical drive. Am Rev Respir Dis 1989;139:1231-1237
- Schwartzstein R, Lilly J, Israel E, Basner R, Sparrow D, Weinberger S, Weiss JW: Breathlessness of asthma differs from that of external resistive loading. Am Rev Respir Dis 1991;141:596 (abstract)
- Scott SM, Walters DA, Singh SJ, Morgan MDL, Hardman AE: A progressive shuttle walking test of functional capacity in patients with chronic airflow obstruction. Thorax 1990;45:781 (abstract)
- Sharp JT in: Roussos C, Macklem P, eds. The Thorax. New York:1985,Marcel Dekker:1155-1203
- Sharp JT, Van Lith P, Nuchprayoon CV, Briney R, Johnson FN: The thorax in chronic obstructive lung disease. Am J Med 1968;44:39-46

- Shore S, Milic-Emili J, Martin JG: Reassessment of body plethysmographic technique for measurement of thoracic gas volume in asthmatics. *Am Rev Respir Dis* 1982;123:515-520
- Silverman M, Barry J, Hellerstein H, Janos J, Kelsen S: Variability of the perceived sense of effort in breathing during exercise in patients with COPD. *Am Rev Respir Dis* 1988;137:206-209
- Simon PM, Schwartzstein RM, Weiss JW, Lahive K, Fencel Vm, Teghtsoonian M, Weinberger SE: Distinguishable sensations of breathlessness induced in normal volunteers *Am Rev Respir Dis* 1989;140:1021-1027
- Simon PG, Schwartzstein RM, Weiss JW, Fencel V, Teghtsoonian M, Weinberger SE: Distinguishable types of dyspnoea in patients with shortness of breath. *Am Rev Respir Dis* 1990;142:1009-1014
- Smart J, Naimi S, Capel LH: The relationship between effort intolerance, spirometry and blood gas analysis in patients with chronic obstructive airway disease. *Br J Dis Chest* 1961;55:6-16
- Snider GL: Changes in COPD occurrence. *Am Rev Respir Dis* 1989;140:S3-S8
- Sorli J, Grassino A, Lorange G, Milic-Emili J: Control of breathing in patients with chronic obstructive lung disease. *Clin Sci* 1978;54:295-304
- DPS Spence and PMA Calverley: Airway reactivity and lung volume in normal and asthmatic subjects *Am Rev Respir Dis* 1992;145:A731
- Stanescu DC, Pattijn J, Clement J, van de Woestijne KP: Glottis opening and airway resistance. *J Appl Physiol* 1972;32:460-466
- Stanescu DC, Rodenstein D, Cauberghs, Wan de Woestijne KP: Failure of body plethysmography in bronchial asthma. *J Appl Physiol* 1982;52:939-948
- Stark RD, Gambles SA, Lewis JA: Methods to assess breathlessness in healthy subjects. A critical evaluation and application to analyse the acute effect of diazepam and promethazine on breathlessness induced by exercise or by raised levels of CO<sub>2</sub>. *Clin sci* 1981;61:429-439
- Stark RD, Gambles SA, Chatterjee SS: An exercise test to assess clinical dyspnoea: estimation of reproducibility and sensitivity *Br J Dis Chest* 1982;76:269-278
- Stevens SS: Issues in psychophysical measurement. *Psychological Review* 1971;78:426-450
- Stockley RA, Finnegan P, Bishop JM: Effect of intravenous terbutaline on arterial blood gas tensions, ventilation and pulmonary circulation in patients with chronic bronchitis and cor pulmonale *Thorax* 1977;32:601-605
- Strain DS, Kinasewitz GT, Franco DP, George RB: Effect of steroid therapy on exercise performance in patients with irreversible COPD *Chest* 1985;88:718-721
- Stubbing DG, Pengelly LD, Morse JLL, Jones NL: Pulmonary mechanics during exercise in normal males: *J Appl Physiol* 1980;49:506-510

- Stubbing DG, Pengelly LD, Morse JLL, Jones NL: Pulmonary mechanics during exercise in subjects with chronic airflow limitation. *J Appl Physiol* 1980;49:511-515
- Supinski GS, Clarey SJ, Bark H, Kelsen SG: Effect of inspiratory muscle fatigue on the perception of effort during loaded breathing. *J Appl Physiol* 1987;62:300-307
- Swidwa DM, Montenegro HD, Goldman MD, Lutchen KR, Saidel GM: Helium-Oxygen breathing in severe COPD. *Chest* 1985;87:790-795
- Swinburn CR, Wakefield JM, Jones PW: Relationship between ventilation and breathlessness during exercise in chronic obstructive airways disease is not altered by prevention of hypoxaemia; *Clin Sci* 1984;67:515-519
- Swinburn CR, Wakefield JM, Jones PW: Performance, Ventilation, and oxygen consumption in 3 different types of exercise test in patients with chronic obstructive lung disease. *Thorax* 1985;40:581-586
- Swinburn CR, Mould H, Stone TN, Corris PA, Gibson GJ: Symptomatic benefit of supplemental oxygen in hypoxaemic patients with chronic lung disease. *Am Rev Respir Dis* 1991;143:913-915
- Taguchi O, Kikuchi Y, Hida W, Iwase N, Okabe S, Satoh M, Chonan T, Inoue H, Takishima T: Effects of airway anaesthesia on dyspnoea during bronchoconstriction and loaded breathing in normal subjects *Am Rev Respir Dis* 1989;139:322
- Tattersfield AE: Effect of beta-agonists and anticholinergic drugs on bronchial reactivity. *Am Rev Respir Dis* 1987;136:S64-S68
- Taylor SM, Pare PD, Armour CL, Hogg JC, Schellenberg RR: Airway reactivity in COPD. *Am Rev Respir Dis* 1985;132:30-35
- Teale C, Morroson JFJ, Jones PC, Muers MF: Reversibility tests in chronic obstructive airway disease: their predictive value with reference to benefit from domiciliary nebuliser therapy. *Respir Med* 1991;85:281-284
- Teculescu DB, Bohdana AB, Peslin R, Pino J, Jansen da Silva JM: Variability, reproducibility and observer difference of body plethysmographic measurements. *Clin Physiol* 1982;127-138
- Teule GJJ, Majid PA: Haemodynamic effects of terbutaline in chronic obstructive airways disease *Thorax* 1980;35:536-542
- Thurlbeck WM: Pathophysiology of Chronic Obstructive Pulmonary Disease. *Clin Chest Med* 1990;11(3):389-403
- Tobin MJ: Respiratory Muscles in Disease. *Clin Chest Med* 1988;9:263-286
- Tukiainenen P, Salorinne Y: Oxitropium, Salbutamol and their combination in asthma. *Eur J Respir Dis* 1985;67:31-36
- Tweeddale PM, Merchant S, Leslie M, Alexander F, McHardy GJR: Short term variability in FEV1: relation to pre test activity, level of FEV1 and smoking habits. *Thorax* 1984;39:928-932

- Tweeddale PM, Alexander F, McHardy GJR: Short term variability of FEV1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. *Thorax* 1987;42:487-490
- Van Lith P, Johnson FN, Sharp JT: Respiratory elastances in relaxed and paralysed states in normal and abnormal men. *J Appl Physiol* 1967;23:475-486
- Vathenen AS, Britton JR, Ebdon P, Cookson JB, Wharrad HJ, tattersfield AE: High dose inhaled albuterol in severe chronic airflow limitation. *Am Rev Respir Dis* 1988;138:850-855
- Vinegar A, Sinnett EE, Leith DE: Dynamic mechanisms determine functional residual capacity in mice, *Mus musculus* *J Appl Physiol* 1979;46:867-891
- Vyas MN, Banister E, Morton JW: response to exercise in patients with airway obstruction. II. Effects of breathing 40% oxygen. *Am Rev Respir Dis* 1971;103:401-412
- Weir DC, Burge PS: Measures of reversibility in response to bronchodilators in chronic airflow obstruction, relation to airway calibre. *Thorax* 1991;46:43-45
- West WW, Nagai A, Hodgkin JE, Thurlbeck WM: The National Institutes of Health Intermittant Positive Pressure Breathing Trial: Pathology studies 3 The diagnosis of emphysema *Am Rev Respir Dis* 1987;135:123-129
- Whitelaw WA, Derenne J-P, Milic Emili J: Occlusion pressure as a measure of respiratory centre output in concious man. *Respiration Physiol* 1975;23:181-199
- Whitelaw WA, McBride B, Ford GT: The effect of lung volume on breathholding. *J Appl Physiol* 1987;62:1962-1969
- Wilson RC, Jones PW: A comparison of the visual analog scale and modified Borg Scale for the measurement of dyspnoea during exercise. *Clin Sci* 1989;76:277-282
- Wright JL, Lawson L, Pare PD et al: The detection of small airways disease *Am Rev Respir Dis* 1984;129:989-994
- Woolcock AJ, Rebusck AS, Cade JF, Read J: Lung volume changes in asthma measured concurrently by 2 methods. *Am Rev Respir Dis* 1971;104:703-709
- Yan K, Salome CM, Woolcock AJ: Prevalence and nature of bronchial hyperresponsiveness in subjects with COPD. *Am Rev Respir Dis* 1985;132:25-29