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Non-invasive Measurement of Respiratory Mechanics and Work of Breathing

Martin Keith Johnson
BA MBChB(Hons) FRCP

Conducted in the Departments of Respiratory Medicine and Anaesthesia in Glasgow Royal Infirmary

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List of Abbreviations

ANOVA	Analysis of variance
AT	Anaerobic threshold
ATP	Ambient temperature and pressure
AU	Arbitrary units
AUC	Area under the curve
BDI	Baseline Dyspnoea Index
BMI	Body mass index
$Borg_{dysp}$	Borg score for dyspnoea
$Borg_{leg}$	Borg score for leg fatigue
BR	Breathing Reserve
BTPS	Body temperature and pressure, saturated with water vapour
BTS	British Thoracic Society
C	Compliance
C_{br}	Central airway wall compliance
C_{CW}	Chest wall compliance
C_L	Lung compliance
CMV	Controlled ventilation
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPI	Composite physiologic index
CRP	Clinical, Radiographic and Physiologic
CRQ	Chronic Respiratory Disease Questionnaire
E	Elastance
ECSC	European Community for Steel and Coal
E_{CW}	Chest wall elastance
EELV	End-expiratory lung volume
E_L	Lung elastance
E_{rs}	Respiratory system elastance
f	Frequency
FEV_1	Forced expiratory volume in 1 second
FOT	Forced oscillation technique
FRC	Functional residual capacity
FVC	Forced vital capacity
GRI	Glasgow Royal Infirmary
HR	Heart rate
HRQOL	Health related quality of life
HRR	Heart rate reserve
I	Inertance

IC	Inspiratory capacity
ICU	Intensive care unit
$IC_{unloaded}$	Inspiratory capacity during unloaded exercise
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IQR	Interquartile range
I_{rs}	Respiratory system inertance
IRV	Inspiratory reserve volume
K_{CO}	Transfer coefficient
LCADL	London Chest Activity of Daily Living Scale
LSMLR	Least squares multiple linear regression
LVRS	Lung volume reduction surgery
MCS	Mental component score of SF-36
MRC	Medical research council
MVV	Maximum voluntary ventilation
NICE	National Institute for Clinical Excellence
NIV	Non-invasive ventilation
NS	Not significant
O_2	Oxygen
O_2 pulse	Oxygen pulse
OCD	Oxygen cost diagram
$P_{(A-a)}O_2$	Alveolar-arterial pressure gradient calculated using P_aO_2 and P_aCO_2
$P_{(A-tc)}O_2$	Alveolar-arterial pressure gradient calculated using $P_{tc}O_2$ and $P_{tc}CO_2$
P_{ao}	Airway opening pressure
P_aO_2, P_aCO_2	Arterial partial pressure of O_2 and CO_2 respectively
P_{br}	Pressure due to breathing waveform in forced oscillation technique
PCS	Physical component score of SF-36
PEEP	Positive end-expiratory pressure
$PEEP_i$	Intrinsic positive end-expiratory pressure
PEF	Peak expiratory flow
P_{fo}	Pressure due to forcing signal in forced oscillation technique
PFT	Pulmonary function test
P_{gas}	Gastric pressure
P_{H_2O}	Partial pressure of water vapour at ambient levels of humidity
P_{musc}	Pressure due to respiratory muscle activity
P_{oes}	Oesophageal pressure
P_{rs}	Driving pressure of the respiratory system
$P_{tc}O_2$, $P_{tc}CO_2$	Transcutaneous partial pressure of O_2 and CO_2 respectively
PTT	Pulse transit time
R	Respiratory exchange ratio
R_{aw}	Airway resistance
R_{int}	Interrupter resistance
R_L	Transpulmonary resistance

ROC	Receiver operating characteristic
R_p	Peripheral airway resistance
RR	Respiratory rate
R_{rs}	Respiratory system resistance
R_{rs6}	Respiratory system resistance measured at 6 Hz
RV	Residual volume
RWV	Respiratory waveform variation
SD	Standard deviation
SEM	Standard error of the mean
SF-36	Short Form-36
sG_{aw}	Specific conductance
SGRQ	St George's Respiratory Questionnaire
S_pO_2	Oxygen saturation by pulse oximetry
STPD	Standard temperature and pressure, dry
T_{amb}	Ambient temperature
TDI	Transition dyspnoea index
t_I, t_E	Array of start times for inspiration and expiration respectively
TLC	Total lung capacity
T_{LCO}	Diffusing capacity
T_{lim}	Duration of loaded cycling in the endurance test
UKAS	United Kingdom Accreditation Service
V	Volume
$\dot{V}$	Flow
$\ddot{V}$	Rate of change of flow
VAS	Visual analogue scale
$\dot{V}_{br}$	Flow due to breathing waveform in forced oscillation technique
VC	Vital capacity
VCO_2	Carbon dioxide output
V_D/V_T	Dead space to tidal volume ratio
V_E	Minute ventilation
V_E/VCO_2	Ventilatory equivalent for CO_2
V_E/VO_2	Ventilatory equivalent for O_2
$\dot{V}_{fo}$	Flow due to forcing signal in forced oscillation technique
VO_2	Oxygen uptake
V_T	Tidal volume
WR	Cycle ergometer work rate
W_{tot}	Total work of breathing
W_{res}	Resistive work of breathing
W_{elas}	Elastic work of breathing
$WOB_{FOT,Z}$	Estimate of resistive work of breathing using oscillometry impedance
$WOB_{FOT,R}$	Estimate of resistive work of breathing using oscillometry resistance
$WOB_{FOT,X}$	Estimate of resistive work of breathing using oscillometry reactance
W_{PEEP}	Work due to intrinsic PEEP

X	Reactance
X_{rs}	Respiratory system reactance
Z	Impedance
Z_{br}	Central airway wall impedance
Z_c	Central impedance
Z_p	Peripheral impedance
Z_{rs}	Respiratory system impedance
Z_{uaw}	Upper airway impedance
Z_w	Chest wall impedance
Δ	Change
θ	Phase
%FL	Percentage flow limitation
$\Delta P_{tc}O_{2,peak}$, $\Delta P_{tc}CO_{2,peak}$	Change in $P_{tc}O_2$ and $P_{tc}CO_2$ between resting state and peak exercise

$_{,area}$	subscript indicating area
$_{,ave}$	subscript indicating average
$_{,CPAP}$	subscript indicating CPAP method for measuring elastance
$_{,diff}$	subscript indicating maximum to minimum difference
$_{,dyn}$	subscript indicating dynamic
$_{,end}$	subscript indicating end-exercise measurement.
$_{,exp}$	expiratory component
$_{,insp}$	inspiratory component
$_{,iso}$	subscript indicating measurement at isotime
$_{,max}$	subscript indicating maximum
$_{,NIV}$	subscript indicating NIV method for measuring elastance
$_{,peak}$	subscript indicating peak measurement
$_{,rest}$	subscript indicating measurement at rest
$_{,st}$	subscript indicating static

LIST OF PUBLICATIONS

Papers

1. Johnson MK, Birch M, Carter R, Kinsella J, Stevenson RD. Use of reactance to estimate transpulmonary resistance. *European Respiratory Journal* 2005;**25**:1061-9.

2. Johnson MK, Birch M, Carter R, Kinsella J, Stevenson RD. Measurement of physiological recovery from exacerbation of chronic obstructive pulmonary disease using within-breath forced oscillometry. Submitted to *Thorax*. March 2006.

Abstracts

1. Johnson MK, Carter R, Birch M, Kinsella J, Stevenson RD. Use of Within-breath Rrs Values at 5Hz to Estimate Resistive Work of Breathing During Histamine Challenge Tests. *European Respiratory Journal* 2002; **20**(Suppl 38):12s.

2. Johnson MK, Higgins MJ, Kinsella J, Stevenson RD. Validation of a Noninvasive Method for Measuring Respiratory System Elastance. *AJRCCM* 2003; **167**:A545.

3. Johnson MK, Carter R, Higgins M, Kinsella J, Stevenson RD. Measurement of elastic work of breathing in the pulmonary function laboratory. *Thorax* 2003;**58**:iii71.

4. Johnson MK, Birch M, Carter R, Kinsella J, Stevenson RD. Use of Reactance to Estimate Transpulmonary Resistance and Resistive Work of Breathing. *European Respiratory Journal* 2004;**24 suppl 48**:576s

5. Johnson MK, Birch M, Carter R, Fuld J, Kinsella J, Stevenson RD. Within-breath Reactance and Bronchodilator Reversibility. *European Respiratory Journal* 2005;**26 suppl 49**:120s

6. Johnson MK, Carter R, Kinsella J, Stevenson RD. Prediction of Progression in Interstitial Lung Disease. Submitted to American Thoracic Society Annual Meeting 2006.

SUMMARY

The mechanical properties of the respiratory system such as resistance, elastance and mechanical work of breathing are rarely measured directly but are inferred from the effect of respiratory disease on maximal lung volumes and flows. Although such tests have proved very useful, they have shortcomings, e.g. changes in lung volumes are poor at detecting progression in interstitial lung disease and correlate only weakly with changes in functional capacity achieved post-bronchodilator in patients with airways obstruction. In addition, measurement of maximal flows and volumes requires active patient cooperation which may not be possible if patients are anxious, breathless, cognitively impaired, have reduced conscious level or are at the extremes of age.

The direct measurement of mechanical properties are of interest as they have an obvious physical interpretation but their usefulness has as yet not been systematically tested. Resistance aside, their measurement is rarely performed as it is invasive, requiring either a sedated patient on controlled ventilation to abolish spontaneous respiratory muscle activity or measurement of oesophageal and gastric pressures.

The aim of this thesis was to explore the feasibility and potential clinical value of non-invasive measurements of respiratory mechanics and work of breathing. The work is presented in three sections:-

- Firstly, conventional methods for measuring resistance, elastance and mechanical work of breathing were reviewed and the methods for the non-invasive approaches to be used were described in detail.
- The results from the non-invasive methods were then validated by comparison with conventional techniques in both ventilated patients and in subjects in the pulmonary function laboratory where oesophageal and gastric manometry were performed.
- Finally the non-invasive methods were evaluated in three clinical scenarios: bronchodilator reversibility testing, assessment of progression in interstitial lung disease and monitoring recovery from exacerbation of chronic obstructive pulmonary disease.

Although not widely applied, the non-invasive measurement of resistance has been available since the 1940s through such methods as body plethysmography, airway interruption and forced oscillometry. The same is not true of resistive work of breathing which currently requires the simultaneous measurement of transpulmonary pressure (by application of oesophageal manometry) and flow. In the first validation study, transpulmonary resistance and resistive work of breathing calculated from oesophageal manometry during histamine challenge tests on asthmatic subjects were compared with forced oscillometry variables. The most significant finding was that transpulmonary resistance was not best predicted by oscillometry resistance but by reactance, which is the oscillometry component calculated from a comparison of pressure and flow which are 90° out of phase. It was also shown that resistive work of breathing could be estimated by a function of reactance and flow.

By contrast, the conventional measurement of elastance and elastic work of breathing remains invasive, requiring sedation and controlled ventilation or oesophageal manometry. Non-invasive techniques based upon patient relaxation or positive pressure breathing were proposed and evaluated in sporadic studies throughout the 20th century. None achieved widespread application because of the combination of poor subject compliance and unwieldy apparatus. In this thesis, two methods for measuring elastance and thereby elastic work of breathing were evaluated by comparison with conventional measurements. The first was a direct translation of the positive pressure method proposed by Heaf and Prime in 1956 where the subject was exposed to a pulse of continuous positive airways pressure lasting several breaths. The second was developed in the 1990s applying the technique of least squares multiple linear regression to estimate mechanical variables by examining the effect on volume and flow of small changes in positive inspiratory pressure on adjacent breaths. Although both methods could predict elastance, the simpler method based on a pulse of continuous positive airways pressure proved the more accurate.

The non-invasive methods were then evaluated in three clinically relevant scenarios.

- Firstly, forced oscillometry variables were compared with conventional pulmonary function tests and exercise testing in the assessment of bronchodilator reversibility of airways obstruction (predominantly chronic obstructive pulmonary disease). Bronchodilators produced measurable changes in plethysmography, oscillometry and exercise test variables. Changes in resting pulmonary function tests were unable to

predict changes in endurance exercise time but several variables (including inspiratory capacity, plethysmographic resistance and oscillometry reactance) had modest associations with change in end-exercise ventilation. Reactance was clearly superior in this regard to oscillometry derived work of breathing and resistance. Of interest, the absence of an improvement in exercise capacity post-bronchodilator was associated with increased ventilatory equivalents, suggesting that bronchodilator was having an adverse effect on the efficiency of ventilation.

- The second study looked at the ability of elastance and elastic work of breathing to detect progression in interstitial lung disease over a twelve month period using both survival and a surrogate score derived from vital capacity, diffusing capacity, endurance exercise time, symptoms and health related quality of life. Changes in endurance exercise test variables (especially ventilatory equivalents for oxygen) and health related quality of life proved the most discriminating and were superior to standard measurements such as vital capacity and diffusing capacity. Elastance and elastic work of breathing did not significantly predict survival although they were associated with worse progression scores.
- The third study assessed the ability of forced oscillometry variables to monitor physiological recovery over six weeks following an exacerbation of chronic obstructive pulmonary disease compared with spirometry, gas exchange, symptoms and health related quality of life. Once again, reactance proved superior to oscillometry resistance and work of breathing conferred no added advantage. Of all outcome measures used, oscillometry variables had the widest association with improvements in dyspnoea and health related quality of life.

PART 1: INTRODUCTION AND METHODS

1.1 The Contemporary Measurement of Respiratory Mechanics

Introduction

The effect of disease on mechanical properties of the respiratory system such as resistance, elastance and mechanical work of breathing is rarely measured directly during routine pulmonary function tests but usually inferred from the effect of the pathophysiology on maximal volumes and flows[1]. For example, the increased elastic recoil or stiffness seen in pulmonary fibrosis is detected by its effect on static lung volumes such as vital capacity (VC) or total lung capacity (TLC). Similarly the increased resistance seen in asthma or chronic obstructive pulmonary disease is deduced from the value of forced expiratory flow in 1 second (FEV_1) and its ratio to VC or from the peak expiratory flow (PEF). These conventional pulmonary function tests are very useful but do have areas of deficiency. Examples include detecting progression in interstitial lung disease which is insensitive when using lung volumes[2] or predicting improvement in functional capacity in chronic obstructive pulmonary disease (COPD) from changes in resting pulmonary function[3]. In addition, measurement of maximal flows and volumes requires active patient cooperation which may not be possible if patients are anxious, breathless, cognitively impaired, have reduced conscious level or are at the extremes of age.

Direct measurements of mechanical properties such as resistance, elastance and work of breathing are attractive in that the physical interpretation of the result is more obvious than inferring changes from volumes and flows. Whilst several techniques are available for quantifying resistance[4], the measurement of elastance and mechanical work of breathing remain invasive and therefore rarely performed. The aim of the work presented in this thesis is to develop, validate and evaluate non-invasive methods for assessment of resistance, elastance and mechanical work of breathing.

Chronology of Measurement of Respiratory Mechanics

Since 500BC when Alcmaeon of Croton postulated that goats breathe through their ears, the understanding of respiratory mechanics has come a long way. Over the following two and a half millennia many individuals contributed to our qualitative understanding of the mechanism of breathing and a useful summary has been provided by Otis[5]. Singling out a few individuals, Galen (130-200AD) described the action of the respiratory muscles and Leonardo da Vinci (1452-1519) drew the analogy between the respiratory system and a pair of bellows. Andreas Vesalius (1514 – 1564) introduced experimentation to this area by resecting the thoracic wall of a dog, but leaving the pleura intact so that lung movement could be observed. By the late 17th century, John Mayow (1640-1679) was able to give a reasonably accurate account of the process and produced a model based on a pair of bellows with a glass window to illustrate the process.

Modern understanding of respiratory mechanics underwent a step change in the early part of the 20th century with the work of Fritz Rohrer (1888-1926). He was a descendant of Bernoulli and his skills lay both in mathematics and quantitative experimentation. His body of work is very relevant to the subjects of this thesis and remains frequently cited[6]. His conceptual breakthrough was to apply Newtonian mechanics to respiratory physiology, i.e. to state that expansion of the lungs requires forces to be exerted to overcome resistance, elastance and inertia. Thereby he analysed and formulated the complex mechanical process of breathing in terms of simple variables such as pressure and volume. His papers encompassed the theory and quantification of such subjects as flow resistance in the airways, pressure-volume relaxation curves and estimation of mechanical respiratory work.

Rohrer's ideas were further developed by his pupils, Neergard and Wirz, but then fell from attention until rediscovery by two American groups of physiologists (Fenn, Bayliss and Robertson) approximately twenty years later. Since then the subject has received continuous attention with many fundamental contributions originating in the decades immediately following the Second World War. One of the principal contributors, Mead[7], has suggested that the three major mechanical concepts demonstrated and to a great extent explained since the 1950s have been pulmonary hysteresis (i.e. the loop of transpulmonary pressure and lung volume), frequency dependence of respiratory mechanics and expiratory flow limitation.

Advancement in respiratory mechanics could not have occurred without the development of techniques for measuring pressure, volume, flow and resistance and a concise chronology of this is given in Table 1.1.1.

Table 1.1.1. Chronology of measurement techniques in respiratory mechanics[5].

Year	Development
1643	Torricelli developed the mercury barometer
1826	Carson was the first to describe measurement of intrapleural pressure and hence elastic recoil in cadaveric animals
1842	Hutchinson developed the spirometer for measuring dynamic lung volumes
1915-1925	Rohrer's major publications
1925	Fleisch introduced the pneumotachograph for measuring flow
1927	Neergard & Wirz develop the interrupter technique for measuring flow resistance
1930s	Development of electrical strain gauges for measuring pressure
1949	Buytendijk popularised estimation of intrapleural pressure using the oesophageal balloon
1956	Dubois developed the body plethysmograph for measuring static lung volumes and airway resistance
1956	Dubois proposed the forced oscillometry technique for measuring respiratory resistance

Contemporary Measurement Techniques

Resistance and Elastance

Definition

The concepts of resistance and elastance of the respiratory system or its component parts (airways and tissues) are most simply defined from the following equation of motion[8]:-

$$P_{rs} = E_{rs}(V - V_0) + R_{rs}\dot{V} + I_{rs}\ddot{V} \qquad \text{eqn 1.1.1}$$

where P_{rs} is the driving pressure

E_{rs} is the elastance of the respiratory system

V is the volume and V_0 the relaxed volume

R_{rs} is the resistance of the respiratory system

$\dot{V}$ is flow

I_{rs} is the inertance

$\ddot{V}$ is acceleration.

At breathing frequencies I_{rs} is negligible[9,10] and the equation simplifies to:-

$$P_{rs} = E_{rs}(V - V_0) + R_{rs}\dot{V}. \qquad \text{eqn 1.1.2}$$

Thus, **resistance** and **elastance** can be interpreted as fixed lumped elements defining the coefficients of proportionality between resistive pressure drop and flow and elastic pressure drop and volume respectively.

This linear, single compartment model is only accurate in normal subjects and then over a small range of values. In practice, elastic and resistive properties of the respiratory system are time and frequency dependent, have nonlinear relationships with flow and volume and are interdependent[11]. This behaviour reflects such physical phenomena as viscoelasticity due to stress adaptation of the tissues[12], plastoelasticity indicating hysteresis of the pressure-volume relationship[13] and time constant inequalities causing gas redistribution[14]. Consequently, values of R_{rs} and E_{rs} defined at any time point by equation 1.1.2 can vary widely over the breathing cycle.

Measurement of Resistance

Of the three variables discussed in this thesis, measurement of resistance is by far the most developed. There are four widely accepted methods for this, namely:-

1. **Oesophageal manometry** to measure intrapleural pressure and transpulmonary resistance, R_L, which is thought to represent the sum of airway and lung tissue resistance[15,16].
2. **Body plethysmography** to measure airway resistance, R_{aw}[17].
3. **Airway interruption** to measure interrupter resistance, R_{int}, which is thought also to give airway resistance[18].
4. The **forced oscillation technique** which gives respiratory impedance, Z_{rs}, from which the resistance, R_{rs}, and reactance, X_{rs}, can be calculated[19,20]. R_{rs} is thought to represent the resistance of airways, lung and chest wall.

Oesophageal manometry is necessarily invasive. Usually, a single result is calculated for each breath by determining the width of the pressure–volume loop at iso-volume, dividing by the difference between inspiratory and expiratory flow and averaging over the breath[4,15]. Alternatively, the same result can be achieved by applying the least squares multiple linear regression (LSMLR) technique to equation 1.1.2[21]. Theoretically, R_L could be calculated continuously to give a value of resistance at each volume point during the breath but in practice the signal to noise ratio is low especially in normal subjects and this approach is not practical.

Body plethysmography is not invasive but does require bulky equipment and the panting manoeuvre required in a sealed box can be difficult and claustrophobic for a patient in a degree of respiratory distress. Each measurement gives a single value of R_{aw} at the lung volume used (usually functional residual capacity) although the measurements can be repeated at different lung volumes.

Interrupter resistance is measured by occluding airflow for 100 ms. This is usually performed only once per breath although techniques for multiple occlusion have been described. The value for R_{int} therefore reflects a spot value of resistance at the point in the breath where the occlusion occurs. With increasing airway obstruction, there is slow equilibration of alveolar and mouth pressure which leads to an underestimate of resistance.

Forced oscillometry is arguably the most versatile of the techniques. Like interrupter resistance, it requires only tidal breathing but, if within-breath analysis is performed, it is able to provide a quasi-continuous value of resistance throughout the breathing cycle. It also suffers from the problem of underestimating resistance with increasing levels of airways obstruction which in this case is due to the shunting effect of extrathoracic airways.

Typical Values of Resistance

The normal value of resistance depends upon the technique used and also the gender and body habitus of the subject. Shorter subjects with lower lung volumes and females will tend to have higher values of resistance. The average normal value would be in the vicinity of 0.15 to 0.2 $kPa.s.L^{-1}$ but could be a factor of 10 larger in patients with severe COPD or asthmatics during a bronchoprovocation test[4,21,22]. A comparison of the four techniques in the same subjects[4] showed similar basal median values but, after resistance was increased by bronchoprovocation, R_{rs} and R_{int} increased less than R_L and R_{aw}.

Measurement of Elastance

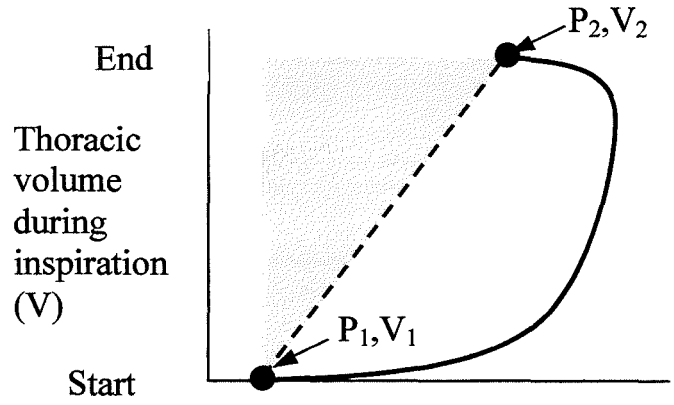
In comparison with resistance, the measurement of elastance is far from a routine measurement. The following approaches are the techniques conventionally used in ventilated and spontaneously breathing patients. Both assume a constant value for elastance over the tidal volume.

1. **Controlled ventilation**

   Airway opening pressure (P_{ao}) and thoracic volume (V) are measured during controlled ventilation (i.e. no respiratory effort) with constant flow inflation[23]. The ratio of the change in pressure to the change in volume between the start and end of inspiration approximates to dynamic elastance ($E_{rs,dyn}$) (see Figure 1.1.1). Static elastance ($E_{rs,st}$) is obtained if end-inspiratory and expiratory occlusions (of 5 seconds) are used. The immediate decay in pressure seen after the end-inspiratory pause is attributable to the phenomena of viscoelasticity[12] and time constant inhomogeneity[14]

which will be discussed in more detail shortly. End-expiratory occlusion is used to determine the level of static intrinsic positive end-expiratory pressure ($PEEP_{i,st}$).

Figure 1.1.1. $E_{rs,dyn}$ measured by controlled ventilation with no pauses.



$$E_{rs,dyn} = \frac{P_2 - P_1}{V_2 - V_1}$$

Several other approaches have been described to measure mechanical properties during controlled ventilation such as passive expiratory relaxation[24], multiple expiratory occlusion[25], supersyringe methods[26,27] and volume recruitment[28]. These differ in the way that resistance is calculated but elastance measurement is essentially the same as the end-inspiratory occlusion method, namely the ratio of change in pressure to volume. The only significant variant to this approach[29,30] has employed multiple linear regression to fit the linear equation of motion (eqn 1.1.2) to the pressure trace obtained during controlled ventilation.

2. Spontaneous Breathing

Dynamic lung elastance ($E_{L,dyn}$) can be determined relatively simply from measurements of oesophageal pressure (P_{oes}) and $\dot{V}$ and is given by the gradient of the line joining points of zero flow on the P_{oes} – V curve[15,31]. Similarly to the case of resistance, a value can also be obtained by applying the LSMLR technique to equation 1.1.2[21]. Measurement of static lung elastance ($E_{L,st}$) also involves measurement of P_{oes} but V is usually determined by a spirometer or body plethysmograph and there is the additional requirement for interruption or breath-holding[32-34]. Static chest wall elastance ($E_{CW,st}$) is conventionally estimated from a prediction equation[35,36]

$$E_{CW,st} = \frac{1}{0.4 \times predictedVC} \quad \text{in kPa.} \qquad \text{eqn 1.1.3}$$

E_{rs}, either dynamic or static, is then given by the sum of these two components:-

$$E_{rs} = E_L + E_{CW}\,. \qquad \text{eqn 1.1.4}$$

It can be seen that this method can only give an approximate value for E_{rs} as E_{CW} is a predicted value and the method cannot be applied in cases where the chest wall is abnormal such as kyphoscoliosis.

Typical Values of Elastance

Over the tidal volume range, E_{CW} and E_L are thought to be of similar size. The widely quoted prediction formula for static respiratory elastance ($E_{rs,st}$) from Agostoni[35,36] where

$$E_{rs,st} = \frac{1}{0.2 \times predictedVC} \quad \text{in kPa.L}^{-1}, \qquad \text{eqn 1.1.5}$$

was derived from data obtained by relaxation methods. In one study of normal adults[37], values for $E_{L,dyn}$ were found to lie in the range 0.30 to 1.12 kPa.L^{-1}. In a further study[31], values of $E_{L,st}$ for young adults were found to be 0.56 to 1.25 kPa.L^{-1}. Theoretically, values for $E_{L,st}$ should be marginally lower than $E_{L,dyn}$ but in normals there is likely to be little difference. By comparison, $E_{rs,st}$ values in anaesthetised normal subjects[38] were found to be 1.45 to 2.39 kPa.L^{-1}. Values for $E_{rs,dyn}$ would be higher, the exact value depending on such variables as tidal volume and respiratory frequency (and thereby the flow rates achieved)[39].

Work of Breathing

Definition

Work is the product of force and distance moved in the direction of the force and is measured in Joules (J). It can alternatively be expressed as the product of pressure and resulting change in volume which is more relevant to the fluid, three-dimensional situation pertaining in the respiratory system.

For the purposes of this thesis, work of breathing is the mechanical work done by the respiratory muscles[40-42]. At its simplest, it can be divided into three components:-

- WORK due to AIRWAY RESISTANCE – work expended against friction in driving gas through the airways
- ELASTIC WORK – energy stored in the chest wall and lungs in an elastic manner during inspiration. During expiration, this energy is used to drive the expulsion of air from the lungs.
- INERTIAL/GRAVITATIONAL WORK – airway gas and lung and chest wall tissues have finite mass and so work must be done when they are accelerated or moved against gravity [9].

In practice there are several further elements contributing to work of breathing namely:-

- WORK due to TISSUE RESISTANCE– this represents the additional resistive work arising from the non-elastic or resistive behaviour of the lungs and chest wall.
- VISCOELASTIC WORK – due to stress adaptation. If an elastic tissue is stretched and held at a new length, the force in the tissue is maximal at first but then falls to a lower, constant value, probably reflecting rearrangements at a molecular level[12].
- PLASTOELASTIC WORK – this is a reflection of elastic hysteresis. Static inspiratory and expiratory pressure-volume plots form loops, the width of which increases with tidal volume. This is principally an effect of surfactant[13].
- WORK DUE TO TIME CONSTANT INEQUALITIES – in diseased lungs, there is heterogeneity of filling of different areas because of variation in mechanical properties. This can be visualised as difference in time constants for different lung units. If inflation is held, the phenomenon of "pendelluft" will be seen where gas redistributes from fast to slow filling units[14,39,43,44].

- WORK DONE TO COMPRESS AND RAREFY AIR – in moving air in and out of the lungs work must necessarily be performed on its compression and rarefaction[45].
- WORK TO ALTER CHEST WALL SHAPE – with increased ventilation, the chest wall shape differs from its passive configuration which leads to additional work[46].
- WORK AGAINST INTRINSIC PEEP – when expiratory time is insufficient, alveolar pressure remains positive at the end of expiration (intrinsic PEEP). This pressure has to be overcome before inspiration can commence and this initial pressure load must be continued throughout inspiration which leads to additional work[47,48].

The relative contribution of each of these components varies between subjects, with breathing pattern and in respiratory disease. For example, intrinsic PEEP and time constant inhomogeneities are absent in healthy lungs, alteration of chest wall shape is only significant with increased ventilation and work done rarefying air becomes significant at high lung volumes, high respiratory rates and at high altitude.

A final concept to be introduced here is that of NEGATIVE WORK which describes the situation seen during expiration where contracting inspiratory muscles are forced to extend by greater opposing elastic forces. Physically this work represents that component of the elastic energy stored in the thorax during inspiration which is subsequently not converted to useful work overcoming resistance during expiration. It is instead converted to heat by the braking action of the inspiratory muscles.

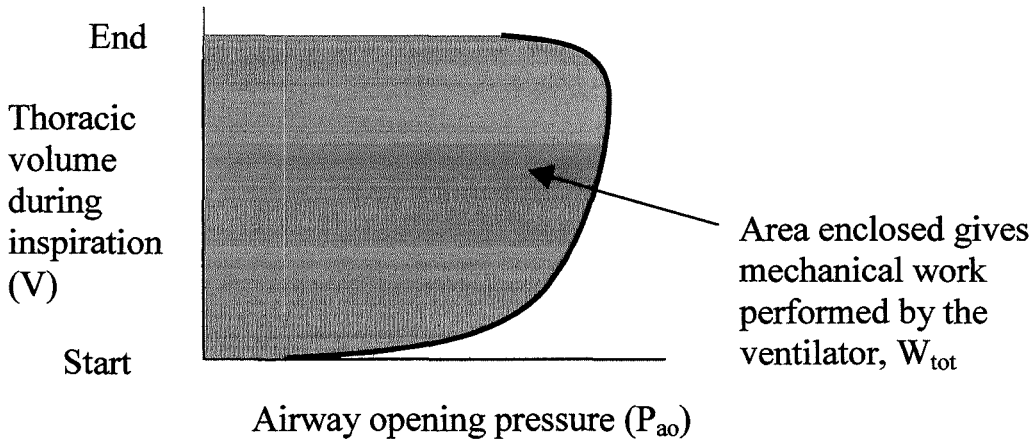
Measurement of Work of Breathing

The conventional measurement of work of breathing is an invasive process. The precise methodology available depends upon the context of the subject.

1. **Ventilated Subjects**

   If the subject is paralysed and on controlled ventilation, the mechanical work of breathing performed by the ventilator (W_{tot}) can be measured from the area within the loop formed by P_{ao} and V during inspiration[38]. This is shown in Figure 1.1.2.

Figure 1.1.2. A typical plot of thoracic volume versus airway opening pressure during the inspiration phase of controlled ventilation.
The area subtended by the pressure-volume curve to the volume axis gives the mechanical work performed by the ventilator. If airway opening pressure is measured at the proximal rather than distal end of the trachea, the work includes that done against the endotracheal tube.



It is possible to partition the work of breathing further as shown in Figure 1.1.3 to estimate resistive work (W_{res}), elastic work (W_{elas}) and work done against intrinsic PEEP (W_{PEEP}).

These areas are given by the following equations:-

$$W_{elas} = \frac{1}{2} E_{rs,dyn} V_T^{\,2} \qquad \text{eqn 1.1.6}$$

$$W_{PEEP} = PEEP_{i,dyn} V_T \qquad \text{eqn 1.1.7}$$

$$W_{res} = W_{tot} - W_{elas} - W_{PEEP} \qquad \text{eqn 1.1.8}$$

where V_T is tidal volume and $PEEP_{i,dyn}$ is dynamic intrinsic PEEP.

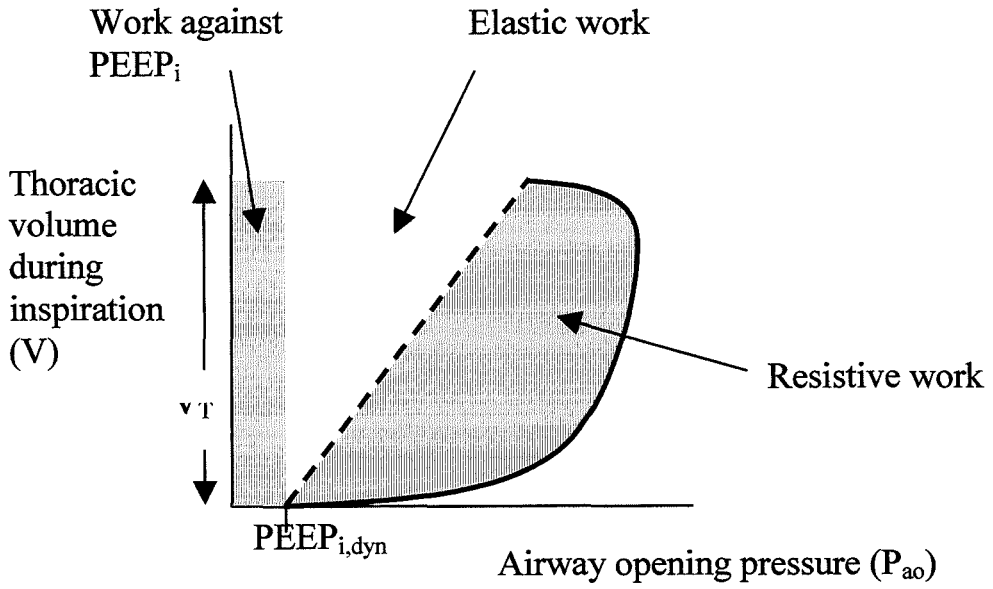
The advantages of this method are that it is easy to perform in ventilated subjects and the elastic properties of the chest wall can be determined because of the absence of respiratory muscle activity. However, the work of breathing measured is that performed by the ventilator and this will not be the same as the work that would be performed if the subject were unsedated and breathing spontaneously because:-

- Work of breathing depends upon the ventilatory flow waveform. This is particularly true of W_{res}, an effect which is augmented by the nonlinear

resistance characteristics of the endotracheal tube[49-53]. $PEEP_{i,dyn}$ is sensitive to any factor which increases tidal volume, reduces expiratory time or lowers thoracic recoil[54]. $E_{rs,dyn}$ and W_{elas} are also affected by changes in breathing frequency, flow and inspiratory waveform but are less sensitive than W_{res}[39,49,52,53,55].

- To exclude the effect of the endotracheal tube, tracheal pressure must be measured[50].
- Anaesthesia alters mechanical properties and therefore work of breathing. It increases elastance and resistance, probably due to reduced functional residual capacity[56].
- During passive inflation, there is little change of chest wall shape[57]. The distortion caused to the chest wall during spontaneous breathing increases elastic work. This component increases with minute ventilation[46] and will not be measured by this technique.

Figure 1.1.3. A plot of thoracic volume versus airway opening pressure during controlled ventilation divided into areas corresponding to resistive work, elastic work and work done against intrinsic PEEP.
V_T is tidal volume. The dashed line joins points of zero flow at the beginning and end of inspiration.



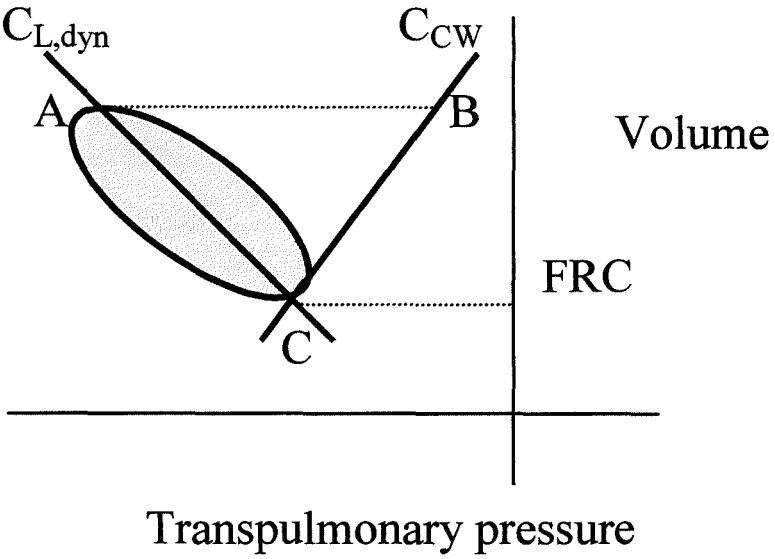
Several variations of this method have been employed to overcome the above problems. In one approach, the work of breathing during spontaneous breathing was estimated by setting the ventilator to mimic a spontaneous pattern of breathing[47,58]. In a second approach, the relative contributions of the ventilator and patient in overcoming the work of breathing were estimated[59]. This required a pressure volume loop to be measured during controlled ventilation in the absence of muscular effort. Then the patient was allowed to make breathing efforts and was placed on a setting (such as assist control ventilation) which enabled prescription of breathing frequency and tidal volume. The pressure volume loop was re-measured and the difference in area between the relaxed and active loops presumed to give the patient's contribution to work of breathing.

2. Spontaneously Breathing Subjects

In this context, the measurement of work of breathing becomes more complex. It is helpful to visualise the process using the Campbell diagram, shown in Figure 1.1.4[60]. To generate the Campbell diagram, transpulmonary pressure is measured during spontaneous breathing. Transpulmonary pressure can be obtained from the difference between pressure in the lower oesophagus (P_{oes}) and mouth or airway opening pressure (P_{ao}). A plot of P_{oes}-P_{ao} against volume generates a loop whose area gives W_{res}. If the points of this loop corresponding to zero flow are joined by a straight line, then the gradient of the line gives the dynamic compliance (compliance is the reciprocal of elastance) of the lung and the loop area is divided into inspiratory and expiratory W_{res}.

Next the static pressure volume relationship of the chest wall is determined. This can be measured accurately by (P_{oes}) measurements during controlled ventilation[61] but this approach is usually not an option unless the patient is already on a ventilator. An alternative technique is to measure (P_{oes}) at different lung volumes whilst the subject relaxes against an occluded airway with an open glottis. This measurement is difficult to perform reliably[35,62]. Many investigators resort to the use of predicted E_{CW} (equation 1.1.3). If a line with a gradient equal to the chest wall compliance is then placed on the Campbell diagram passing through the end-expiratory point where flow is zero, then W_{elas} is given by the triangular area between the compliance lines of the lung and chest wall.

Figure 1.1.4. The Campbell diagram.
The loop shows transpulmonary pressure during spontaneous breathing and its area gives W_{res}. $C_{L,dyn}$ is the line joining points of zero flow and its gradient gives dynamic lung compliance. (Compliance is the reciprocal of elastance). C_{CW} is a line with gradient equal to the static chest wall compliance (determined elsewhere) and placed on the graph to intersect with $C_{L,dyn}$ at FRC, the functional residual capacity. The triangular area ABC gives elastic work of breathing.

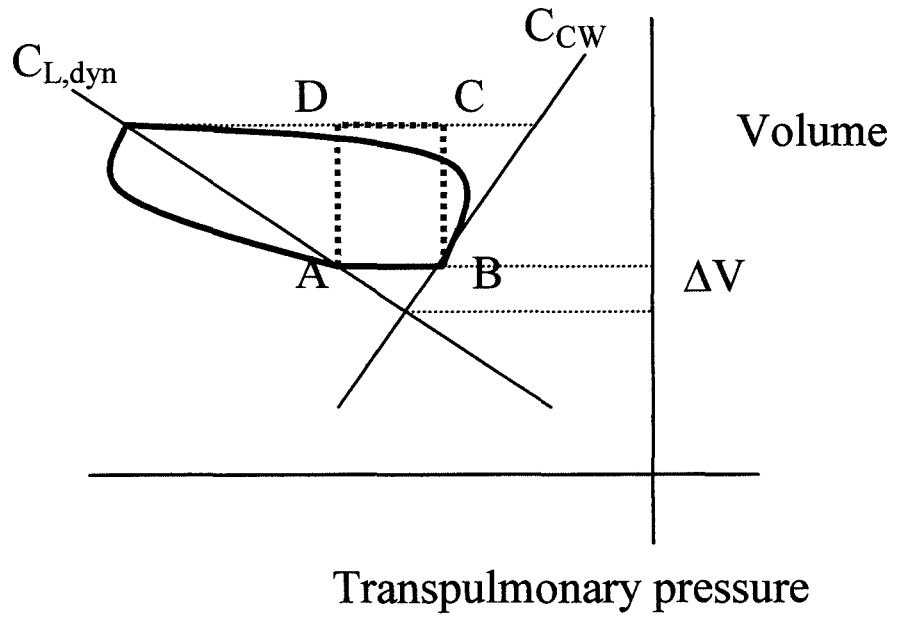


If $PEEP_{i,dyn}$ is present, then the effect of this on the Campbell diagram is shown in Figure 1.1.5 and W_{PEEP} can be calculated from this diagram or from equation 1.1.7. The optimum way to determine $PEEP_{i,dyn}$ in a spontaneously breathing subject has not yet been determined[63]. The simplest way to measure it is by the fall in intrapleural pressure at the end of expiration before inspiratory flow commences. However, this approach is only valid if expiratory muscles are relaxed. If not, then several means of correcting the value using gastric pressure measurements have been proposed[64-67]. Use of the Campbell diagram can be further complicated (e.g. by significant expiratory muscle activity or chest wall distortion during increased ventilation) and a more detailed analysis is given by Roussos and Campbell[41].

The Campbell Diagram method has the advantage that it does not require paralysis and ventilation but it is again invasive, requiring oesophageal and perhaps gastric pressure measurement. A significant problem is the need to use predicted values for $E_{CW,st}$

which limits its applicability to subjects with a normal chest wall at a normal FRC. In addition, work due to resistance of the chest wall tissues is completely neglected. Finally a problem common to all techniques using measurement of volume or flow at the mouth is error introduced due to gas compressibility as the volume change actually produced by the respiratory muscles is that occurring in the lungs[45].

Figure 1.1.5. The effect of $PEEP_{i,dyn}$ on the Campbell diagram.
The compliance lines no longer intersect at the point of zero flow at end-expiration. Instead, they are separated at this point by a pressure difference equal to $PEEP_{i,dyn}$ (distance AB). The volume of this line above FRC (ΔV) represents dynamic hyperinflation. W_{PEEP} is given by the rectangular area ABCD.



Typical Values

There are no published reference values or prediction equations for work of breathing but there are studies measuring it in several different clinical conditions. Comparing values between studies is difficult for several reasons:-

- variation in the subjects' condition, e.g. stable or exacerbated chronic obstructive pulmonary disease.

- variation in the subjects' context e.g. paralysed and ventilated, ventilated but not paralysed or spontaneously breathing
- variation in the details of measurement or analysis. If measured during controlled ventilation, what were the ventilator settings (which may not have been standardised during the study) and was tracheal pressure measured to eliminate the resistance of the endotracheal tube? If the Campbell diagram was used, how was chest wall elastance dealt with (e.g. a predicted value or construction of static oesophageal pressure volume curves)? In some studies the chest wall was ignored and work was measured using both the inspiratory and expiratory areas of the oesophageal pressure volume loop.
- variation in the units used, e.g. work per breath ($J.breath^{-1}$), work per unit respired volume ($J.L^{-1}$) or work per unit time ($J.min^{-1}$).

Table 1.1.2 illustrates work of breathing values available for adults from the literature. Unless otherwise specified the values are means for the groups calculated using the techniques described earlier.

Table 1.1.2. Work of breathing values

	W_{tot} $J.L^{-1}$	W_{tot} $J.min^{-1}$	W_{res} JL^{-1}	W_{elas} $J.L^{-1}$	W_{PEEP} $J.L^{-1}$
Normals					
Controlled ventilation (CMV)[47]	0.61		0.23	0.38	
Campbell diagram					
Fessler[68]	0.69	6.37			
Jennings[69]		6.06	1.14 ($J.min^{-1}$)	4.92 ($J.min^{-1}$)	
Schonhofer[70] – *note (1)*	0.48				
Montravers[71] – *note (1)*	0.36	3			
COPD					
CMV / exacerbation[47]	1.37		0.57	0.58	0.42
Campbell diagram					
Exacerbation 1-3 days					
On CPAP[72]	2.26	57.1			
On NIV[72]	1.61	35.3			
Girault[73]	1.89	17.06			
Exacerbation – weaning[74]	1.61	17.37	0.76	0.89	
Exacerbation at 1 week[75]	1.13	8.14			
Stable COPD					
Normocapnic[76]	0.73	7.6			
Hypercapnic[76]	1.03	6.3			
Schonhofer[70] – *note (1)*	0.85				
LVRS[77] – *pre* – *note (2)*	1.42				
- *post*	1.03				
Asthma[78] – pre challenge	0.56	6.2	0.11	0.45	
- peak challenge	2.45	32.1	0.67	1.78	
Cystic fibrosis[79]		12.6	5.1 ($J.min^{-1}$)	7.6 ($J.min^{-1}$)	
Obesity[80]	1.3		0.24	1.06	
Heart Failure[81]	1.3	18	0.45	0.75	
Restrictive Lung Disease[82]	1.98	22.9			
Motor Neurone Disease[83]	0.7	5.7			
Sedation (IV midazolam) [71]	1.04	6			
Ascites[84]	1.15		0.15	1.0	
Tracheostomy[85] - pre	0.92		0.48	0.44	
- post	0.65		0.27	0.38	

Notes

1. These values were determined from the integral of the oesophageal pressure – volume loop and chest wall elastance was disregarded.
2. Lung volume reduction surgery

Why Measure Work of Breathing?

Whilst the physical significance of resistance and elastance is generally obvious, the concept of work of breathing is more complicated. Work of breathing gives in one value a global indication of the state of the mechanical properties of the respiratory system, which can be partitioned into resistive and elastic components. The units in which it is expressed determine its precise physical significance[86]. If summed over a minute and normalised by minute ventilation ($J.L^{-1}$), it closely reflects the mechanical properties of elastance and resistance. If expressed per unit time ($J.min^{-1}$), it represents rate of doing work or power and tracks changes in minute ventilation.

Work of breathing even when expressed in $J.min^{-1}$ is unlikely to give information about the likelihood of developing respiratory muscle fatigue which is much better predicted by a pressure time product[87]. Work of breathing is not the same as oxygen cost of breathing, which is the oxygen and hence energy consumption of the respiratory muscles. The ratio of work of breathing to oxygen cost gives the mechanical efficiency of breathing and many factors affect this ratio. Work of breathing does not include isometric work which has an energy cost but no volume change despite the generation of pressure. Similarly two breaths which have the same volume and pressure changes but different duration will incur different energy costs although the same mechanical work is performed. The timing and nature of the load on the respiratory muscles also affects efficiency with expiratory and resistive loads requiring greater energy costs for the same mechanical work compared with inspiratory and elastic loads[88,89]. Also working at a higher lung volume impairs efficiency[90].

Despite the invasive process involved, interest in the measurement of work of breathing has been sufficient for it to have been reported in several hundred studies. Unsurprisingly, the frequency of this increased with the introduction of a dedicated monitor for performing the measurement[91]. Owing to the accessibility of the measurement during anaesthesia, the largest single group of studies has used work of breathing as an outcome measure for assessing ventilation strategies[92-97].

Other uses in respiratory failure requiring ventilatory support have been to assess the mechanical work imposed by the ventilator circuitry (different ventilators[98], heat and moisture

exchangers[99], nebuliser fittings[100], PEEP valves[101], breath triggering settings[102], endotracheal tubes and laryngeal masks[103]) and to predict when to extubate a patient. An objective approach to the weaning of patients from ventilators has been sought for many years but still proves elusive[104]. Threshold values have been proposed below which it is deemed safe to extubate regardless of other factors such as tachypnoea but these have been derived from retrospective analyses[105-107]. Use of work of breathing values in the decision to extubate has been studied[108,109] but not in an appropriately randomised and controlled manner. Whilst work of breathing has shown a degree of promise in these studies, it is not likely to be sufficient on its own because, as described earlier, it is relatively weakly associated with oxygen cost of breathing.

The impact of treatment strategies on work of breathing is an obvious application for this measurement and this has been most clearly illustrated in subjects with COPD. The application of PEEP or CPAP in ventilated subjects with COPD is complex and work of breathing has been helpful in both demonstrating benefit and providing insight into the mechanism by which it has its effect[110,111]. More recently CPAP and positive pressure ventilation (NIV) have been applied non-invasively using face masks and their effects studied in both acutely unwell[72] and stable subjects with COPD[76] It proved possible to demonstrate that both CPAP and NIV reduced work of breathing but only NIV improved ventilation. Work of breathing has been used to assess the impact of a number of other treatments in COPD including helium-oxygen mixtures[112], bronchodilators[113], blood transfusions in anaemic patients[70], PEEP during exercise[114,115] and the effect of epidural anaesthesia[116,117]. One of the few groups studied serially has been patients following lung volume reduction surgery to document longitudinal postoperative trends[77]. Beyond COPD, the study populations whose work of breathing has been measured form an eclectic collection, the range of which is summarised in Table 1.1.2.

In conclusion work of breathing has been used with some success as a short-term outcome variable for the effect of an intervention which is likely to alter respiratory mechanics. A potential application not yet investigated is that of serial measurements to assess longitudinal change in respiratory disease, the obvious problem with this being the invasive nature of the measurement process.

Thesis Aims

The work covered in this thesis is the further development and testing of techniques for the non-invasive measurement of mechanical properties such as resistance, elastance and work of breathing. Proposal and development of the new methods together with the equipment used to measure them are described in Chapter 1.2.

The validation work is covered in Section 2. In the first part, a novel means of utilising forced oscillometry variables is used to measure resistance and resistive work of breathing. In the second part, elastance and elastic work of breathing are measured using changes induced by positive airway pressure delivered from modern non-invasive ventilators. In both cases validation is by comparison with the conventional invasive measurements described in this introduction.

In Section 3 the new techniques are evaluated in contexts where there are deficiencies with current pulmonary function tests. In bronchodilator reversibility testing and documenting recovery from exacerbation of COPD, the usefulness of resistance and resistive work of breathing are assessed. In longitudinal measurements in interstitial lung disease, elastance and elastic work of breathing are more relevant. Comparison in these studies is with the pulmonary function tests conventionally used in the area.

1.2 Non-invasive Methods for Measuring Respiratory Mechanics

Introduction

This chapter describes the theory and application of the non-invasive methods proposed for measuring respiratory mechanics. As measurements of resistance and elastance were required to determine the respective components of work of breathing, these are not described separately but have been included in the discussion of work of breathing. In developing these methods, it was the intention that they should be as widely applicable as possible. Ideally, a passive test was required, capable of being performed in patients unable to cooperate with active manoeuvres, and the result should be continuous and real-time, analogous to the measurement of pulse oximetry, or at least measurable on a breath by breath basis. The test should be quick to perform and feasible for patients in respiratory failure, both off and on ventilation. The equipment should be portable to allow measurement in immobile patients and it should allow partitioning of the value into resistive work, elastic work and work done against intrinsic PEEP. As will be seen, some but not all of these requirements have been met.

There were no pre-existing systems for performing these measurements "on the shelf". Hence, the development of these methods involved:-

- devising the method of measurement
- assembly of the equipment for performing the measurement which in some cases required the commissioning of its construction
- writing software to convert the measured data into mechanical parameters.

Resistive Work of Breathing

Theory for Non-invasive Measurement

From the Campbell diagram, W_{res} is given by the area within the loop formed by transpulmonary pressure and volume. Mathematically, this can be expressed as

$$W_{res} = \int (P_{oes} - P_{ao})\dot{V}dt . \qquad \text{eqn 1.2.1}$$

This measurement is invasive because of the requirement to measure P_{oes}. At any moment in time, P_{oes} is related to $\dot{V}$ by the following expression

$$P_{oes} - P_{ao} = \dot{V}R_L \qquad \text{eqn 1.2.2}$$

where R_L varies throughout the breathing cycle and is a complex function of $\dot{V}$ and V. It represents resistive contributions from airways and lung tissue. Substituting from eqn 1.2.2 into 1.2.1, the expression for resistive work becomes

$$W_{res} = \int \dot{V}^2 R_L dt \qquad \text{eqn 1.2.3.}$$

This expression no longer contains P_{oes} but R_L instead (which is normally derived itself from P_{oes}). If R_L is replaced by a value of resistance from one of the alternative methods which does not require measurement of P_{oes}, then a non-invasive method of estimating W_{res} becomes possible.

Of the four techniques for measuring resistance described in Chapter 1.1, forced oscillometry was the most attractive for fulfilling this role. It is a passive measurement requiring only tidal breathing and can be performed by unconscious or uncooperative patients or children. The measurement is quick to perform (useful data are available from recordings of less than one minute's duration) and it can give a quasi-continuous, within-breath value of resistance available in real-time if required. Two problems were envisaged with this approach. Firstly, oscillometry resistance, R_{rs}, is thought to represent resistance of the total respiratory system including the resistive contribution from the chest wall. For normal subjects it would therefore exceed R_L by a small amount. Secondly, a well-recognised feature of forced oscillometry when delivered by mouthpiece or facial mask is the upper airway wall shunt[118]. As the degree of distal airways obstruction increases, more of the forcing signal is dissipated in the upper airway wall which leads to R_{rs} increasingly underestimating true respiratory system resistance. Solutions to this problem have included attempts to correct R_{rs} by separate

estimation of upper airway wall shunt resistance with a Valsalva manoeuvre and using it as a correction factor[118]. Alternatively, a head plethysmograph technique has been used to apply the forcing signal to the exterior of the neck and head as well as the airway by using a box sealed at the neck[119]. The former is a difficult voluntary manoeuvre and inaccurate, the latter is too cumbersome. A further suggestion to navigate this problem is to use other oscillometry parameters which are less sensitive to the upper airway shunt, such as admittance (the reciprocal of impedance)[120]. This approach is the more attractive and will be developed further in later chapters.

Forced Oscillation Technique: the Method

The forced oscillation technique (FOT) was first described by Dubois in 1956[19,20]. It requires the excitation of the respiratory system at a frequency higher than the breathing rate and impedance is deduced from the system's response. To achieve this, the subject performs tidal breathing on a mouthpiece or through a face mask. The air which the subject breathes contains a sound wave (a forcing signal) which can be single or multi-frequency. Pressure and flow are measured at the mouth. The composite waveforms obtained are then separated into breathing waveforms and the forcing signal (see Figure 1.2.1). The forcing signals for pressure and flow are combined, usually in the frequency domain using Fourier transform theory, to give impedance (Z_{rs}) and phase (θ) as a function of frequency. These quantities can be converted into resistance (R_{rs}) and reactance (X_{rs}).

Typical results for a normal subject are shown in Figure 1.2.2. The simplest physical interpretation of these results is obtained by assuming that the respiratory system obeys a linear, three component model of resistance (R), elastance (E) and inertance (I)[121] as in equation 1.1.1:-

$$P = EV + R\dot{V} + I\ddot{V}. \qquad \text{eqn 1.2.4}$$

Then

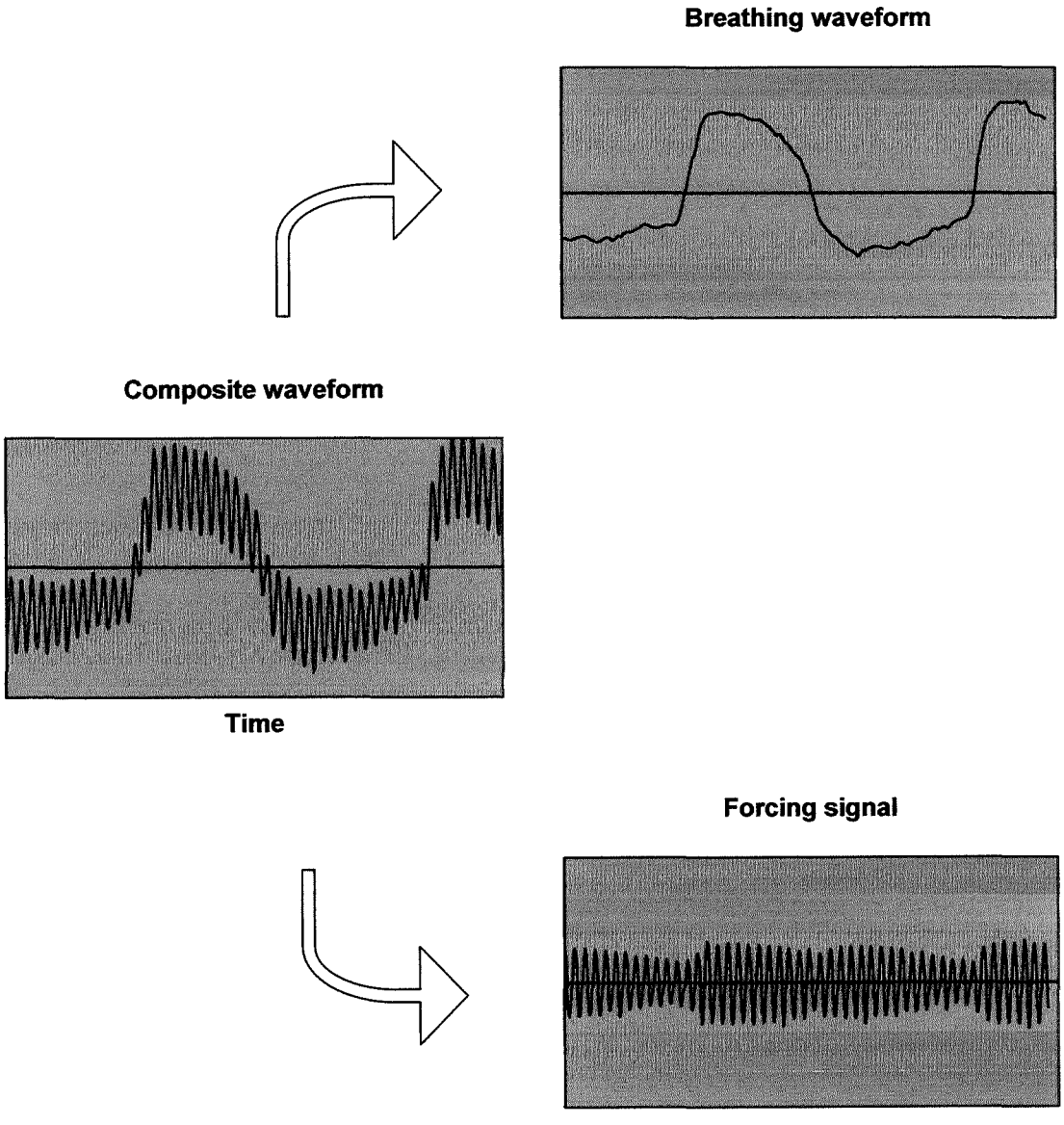
$$R_{rs} = R \qquad \text{eqn 1.2.5}$$

and

$$X_{rs} = 2\pi fI - E/2\pi f \qquad \text{eqn 1.2.6}$$

where f is the forcing frequency. So in a normal subject R_{rs} is equivalent to resistance of the respiratory system and is independent of frequency whereas X_{rs} is a combination of elastance and inertance and is frequency dependent.

Figure 1.2.1. Composite flow waveform measured at the mouth during the forced oscillation technique.
This is then separated into breathing waveform and forcing signal using a moving average technique.



In the presence of respiratory disease, R_{rs} increases in value and acquires frequency dependence whilst X_{rs} decreases (see Figure 1.2.3). The degree of change seen depends upon

the type and severity of the respiratory disease but the pattern is generally the same[122-126]. Debate continues as to the underlying physical process responsible for this behaviour (e.g. lung inhomogeneity[127], upper airway shunt[118], compliance of intrathoracic airways[128]) and hence the correct mathematical model with which to interpret these changes.

Figure 1.2.2. Typical FOT results for a normal subject presented in the frequency domain.

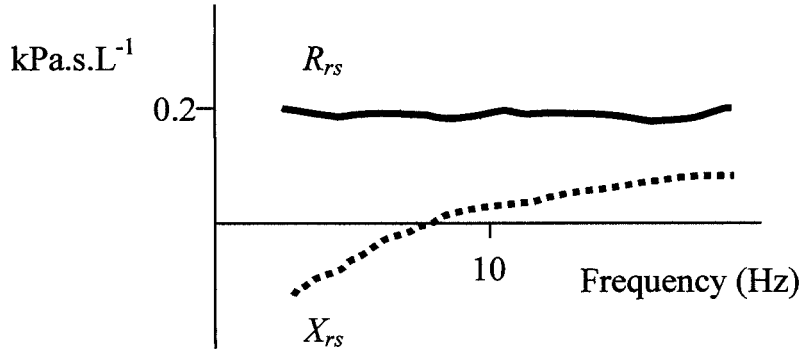
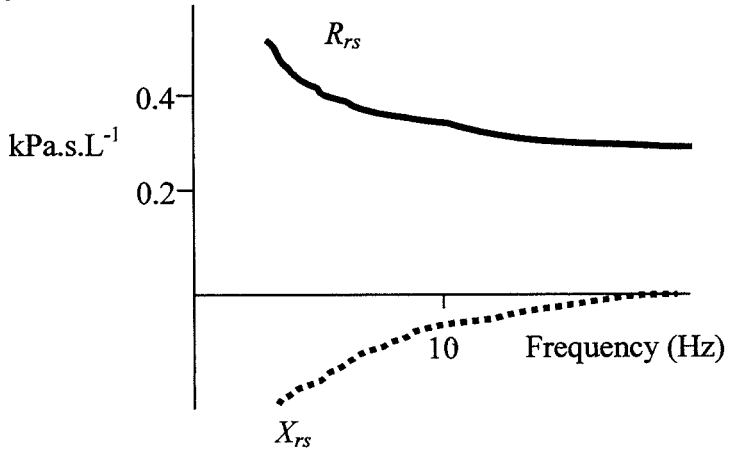


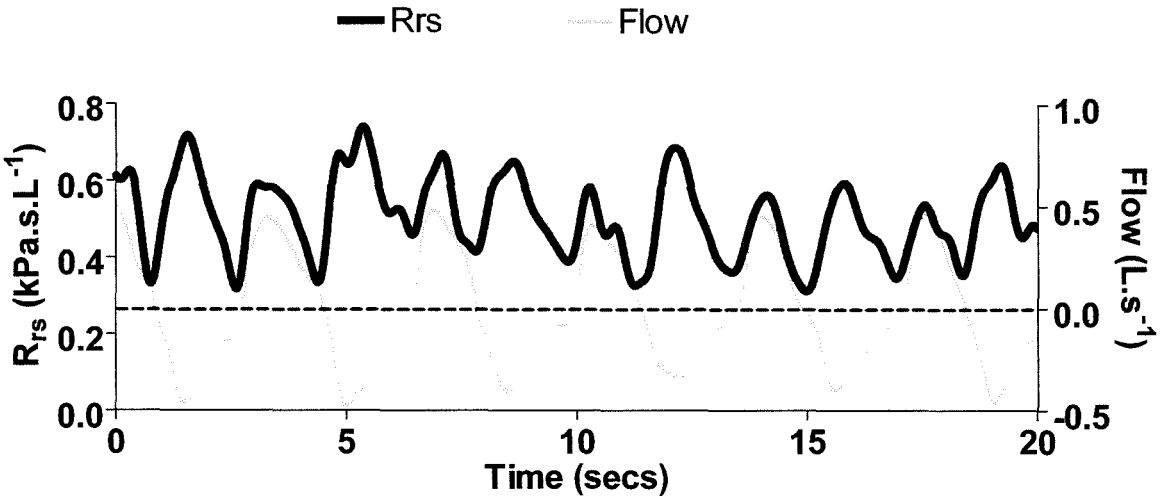
Figure 1.2.3. Typical FOT results for a subject with respiratory disease presented in the frequency domain.
Relative to a normal subject, these show increased R_{rs} with negative frequency dependence and decreased X_{rs}.



The conventional presentation of FOT results is in the frequency domain and involves the averaging of results over a number of breaths[20]. The data can alternatively be measured and analysed to give a continuous value for Z_{rs} over time as shown in Figure 1.2.4[129-133]. This is more successfully achieved using a single excitation frequency rather than a range. The Z_{rs} trace usually shows minima at points of zero flow whilst maxima occur at peak flow. This

variation during the respiratory cycle is due to a combination of factors, such as the relative contributions of laminar and turbulent flow (the latter makes Z_{rs} flow dependent), change in airway calibre as lung volume increases or decreases and variation in glottic aperture size[132].

Figure 1.2.4. Typical within-breath FOT values for R_{rs} from a subject with mild airways obstruction.
Flow below the zero axis is expiratory. Note that the minima in R_{rs} correspond with points of zero flow.

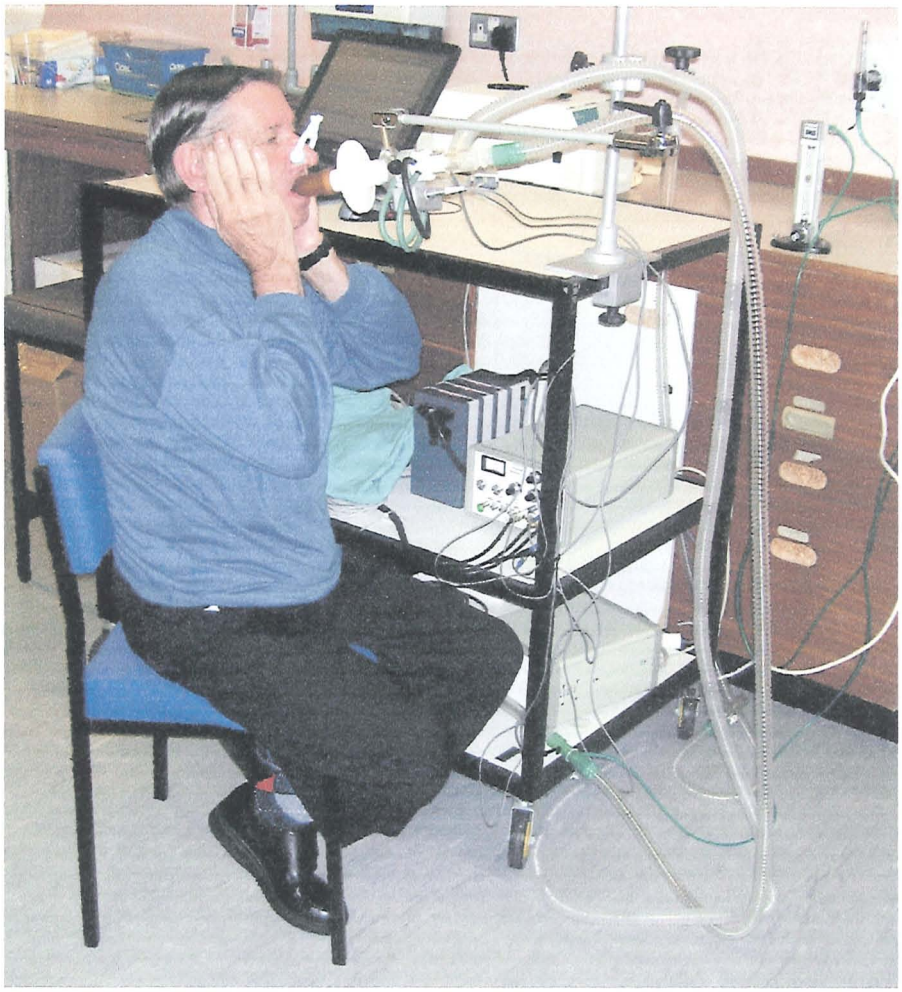


Forced Oscillation Technique: Equipment

For the purposes of this study, it was decided to apply the technique using a single excitation frequency to enable the calculation of within-breath values of Z_{rs} and using as low a frequency as possible (i.e. in the range 5-8 Hz) to minimise the degradation of R_{rs} values by upper airway wall shunt. Commercial devices (e.g. Jaeger Toennies Masterscreen IOS, D-97204 Hoechberg, Germany; SensorMedics R.O.S. Oscilink, Yorba Linda, CA 92887-4645 USA) use multiple frequencies and produce an analysis in the frequency domain although they can be modified to give limited temporal data as a non-standard option. Several groups have therefore developed their own devices for within-breath Z_{rs} measurement[134,135]. The machine used in these studies is a copy of that described by Birch[135], which was built in the Royal London Hospital and measures within-breath Z_{rs} using a single excitation frequency of 5 Hz. It is a portable device (on a trolley) with good reach for the transducer head enabling use by immobile bed bound patients. In addition there is direct access to the raw

measurements allowing great flexibility for data processing. A picture of the device in use is shown in Figure 1.2.5 and the layout shown schematically in Figure 1.2.6.

Figure 1.2.5. The forced oscillometry equipment used in these studies.

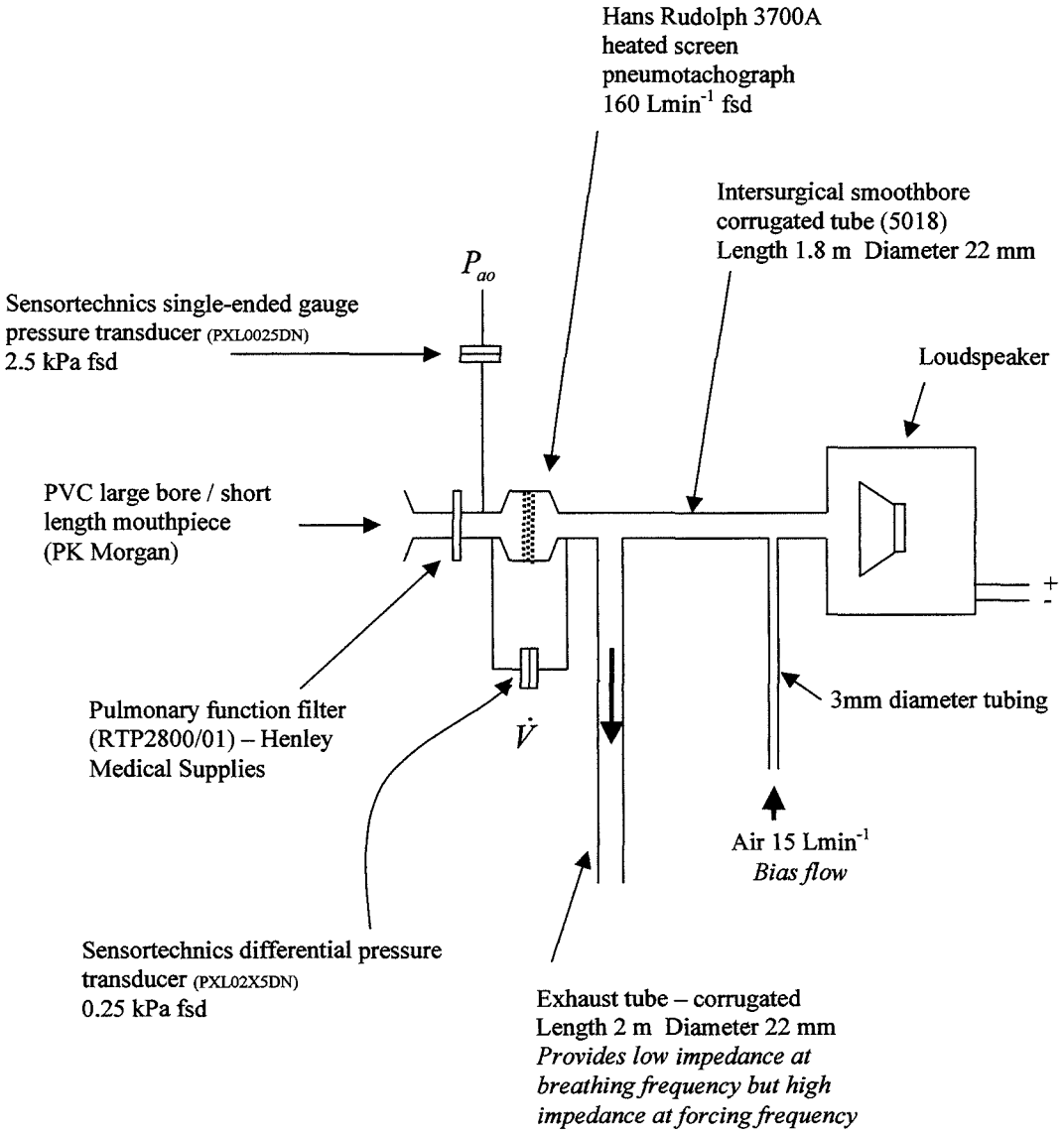


The most recent statement of the technical requirements for forced oscillometry devices was written in 2003[20]. The recommendations are summarised in Appendix 1 together with the performance of the device used in this study.

The biological filter used throughout the studies with FOT was pulmonary function filter model RTP2800/01 (Henleys Medical Supplies Ltd., Welwyn Garden City, Hertfordshire, UK). The 5 Hz impedance of this in combination with the PVC mouthpiece was measured in each subject using the FOT device and found to have mean (±SD) R_{rs} of 0.041 (±0.002)

kPa.s.L^{-1} and mean (±SD) X_{rs} of 0.0128 (± 0.0008) kPa.s.L^{-1}. These values were then used to correct in software the measured impedance of the study subjects as recommended[20].

Figure 1.2.6. Schematic layout of the forced oscillometry device.



Calibration of the FOT device was checked before use on every day on which measurements were taken. Pressure calibration was checked at three points (±1000 Pa, 0 Pa) using an electronic pressure meter (Comark C9551, Comark, Stevenage, UK). Flow calibration was checked at three points (±0.25 L.s^{-1}, 0 L.s^{-1}) using a rotameter (Platon Instrumentation, Bramley, UK). As confirmation, volume calibration was also checked using a 3-litre calibration syringe (MultiFlow, Pulmonary Data Service Instrumentation, NIST accredited

calibration, Louisville, Colorado, USA) and the values accepted if within 50 ml accuracy. Three standard resistors were used to check resistance calibration, namely 0.2, 0.38 and 2.0 kPa.s.L^{-1} (see Appendix 1). Impedance of a normal biological control (MKJ: mean (SD) R_{rs} = 0.293(0.025) kPa.s.L^{-1}, mean (SD) X_{rs} = -0.036(0.009) kPa.s.L^{-1}) and the resistance of mouthpiece and filter combination were measured on all days that the equipment was used.

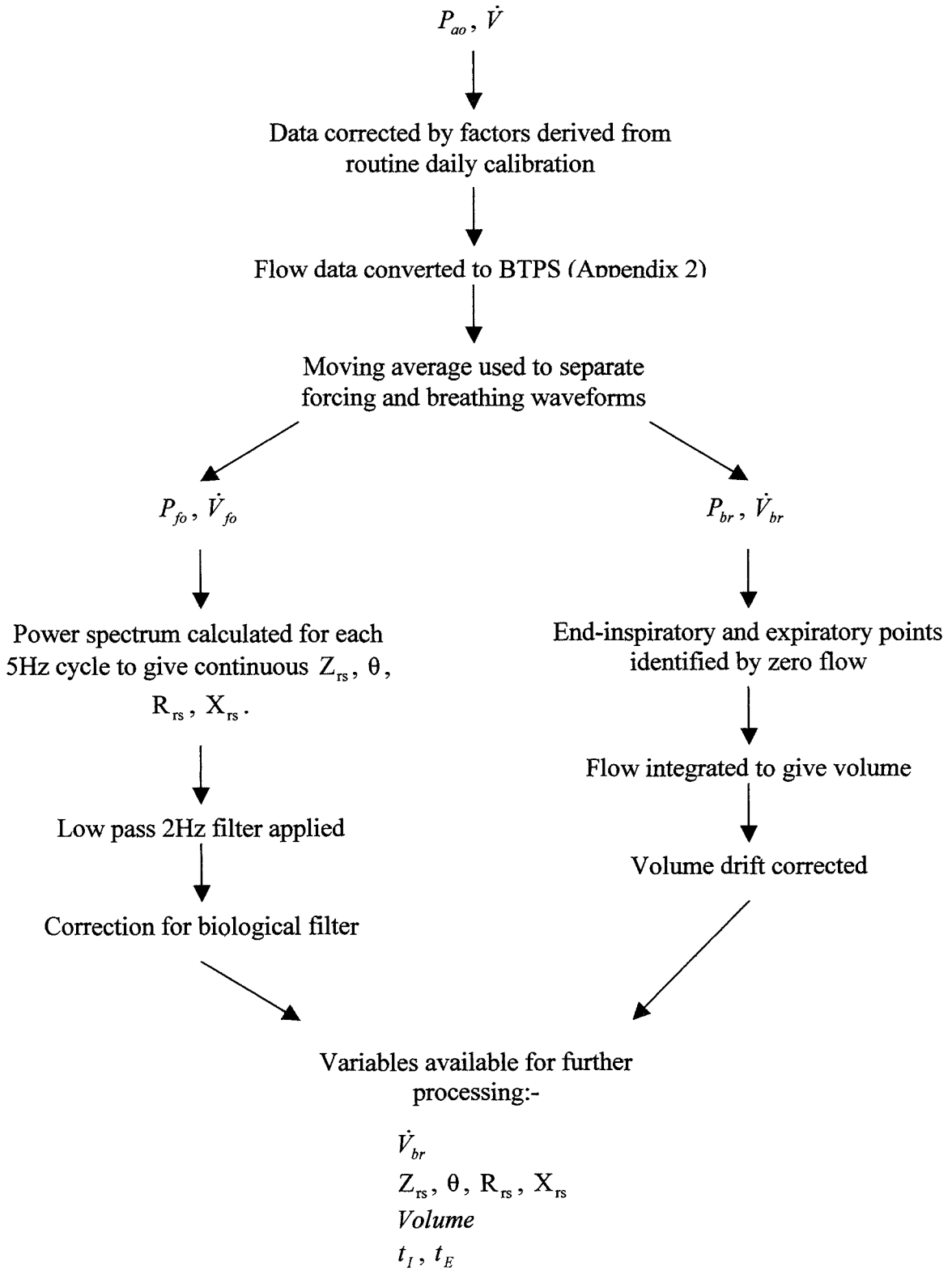
Measurements were performed seated with the neck slightly extended. The subjects wore noseclips, supported their cheeks with their hands and were instructed to breathe normally. When the subject was comfortable on the mouthpiece and the volume trace was stable (a minimum of 30 seconds), the oscillometry measurement was made. The measurement period was 1 minute and at least two measurements were recorded with the subject off the mouthpiece between measurements. Obvious artefacts due to swallowing, glottis closure, leaks were visible via the flow signal and, if extensive, the measurement was repeated.

P_{ao} and $\dot{V}$ were passed from the FOT device into two channels of an analogue to digital (A/D) data acquisition system (MP100A, BIOPAC Systems Inc., Goleta, CA, USA). The signals were then digitised with 16-bit resolution at a sampling rate of 200 Hz and displayed and stored on an IBM-compatible PC using software specific to the above acquisition system (AcqKnowledge 3.7, BIOPAC Systems Inc.). This frequency is much larger than twice the maximum frequency of importance (i.e. 10 Hz) which is that strictly required by the Shannon Sampling Theorem/Nyquist Criterion to define a sinusoidal signal of 5 Hz. To calculate within-breath Z_{rs}, it is necessary to perform a Fourier transform within each 5 Hz cycle. The high sampling rate gives 40 data points within each 5 Hz cycle which gives reasonable within breath resolution of Z_{rs}.

Forced Oscillation Technique: Software Algorithm

P_{ao} and $\dot{V}$ data were analysed in software using the MATLAB numeric computing environment (MATLAB v6, The MathWorks Inc., Natick, MA, USA), which is designed specifically for vector and matrix manipulation and signal processing. The sequence of events in the software algorithm used for the FOT results is summarised in Figure 1.2.7 and the details amplified in the text when necessary.

Figure 1.2.7. Outline of the algorithm used to analyse the FOT results.
The subscripts *fo* and *br* refer to the forcing and breathing waveforms respectively. t_I and t_E are arrays containing the start times of inspiration and expiration for the breaths in the measured data.



The process of separating the breathing and forcing waveforms employed a moving average filter[129], which used the principle that the average over one cycle of a sine wave is zero. If the composite waveform is averaged over 0.2 s (one complete 5 Hz cycle) spanning a particular time point, the contribution from the 5 Hz forcing signal is zero and the result is the breathing waveform at that point. This can then in turn be subtracted from the original composite waveform to deliver the forcing signal at that point. This process can be repeated at each time point along the composite flow waveform and is in essence a filter. With an even number of data points in one cycle of the forcing signal, this filtering process causes a phase shift equivalent to half of the sampling interval (i.e. 2.5 ms) which can be corrected by linear interpolation of adjacent data points.

The algorithm for generating impedance values from the forcing signals was developed and refined in the 1970s and 1980s and is not simply the process of dividing the pressure signal by the flow, although such analysis in the time domain can be done for single frequency results[136-138]. A more convenient way to generate impedance results is to use a method based upon Fourier transforms and power spectra first proposed in 1975[118]. The Fourier transform (FT) is a method for determining the frequency content of a time-varying signal, i.e. data expressed as a function of time are converted to a function of frequency. The results of FTs are complex numbers (i.e. they have a real (A) and imaginary (B) part and are usually expressed in the form, $A + jB$, where $j = \sqrt{-1}$). Power spectra are generated by multiplying an FT result by the complex conjugate of a second FT. Auto-spectra are power spectra where the two FTs are the same and cross-spectra are power spectra where they are different. The importance of auto-spectra is that they are real numbers and give the power of a time varying signal as a function of frequency. By contrast, cross-spectra are generally complex and yield the phase information between two time varying signals. Whilst impedance can simply be calculated by the ratio of the FTs for pressure and flow, power spectra are used instead because this minimises the errors involved in the process[139,140].

Both the magnitude ($|Z_{rs}|$) and phase (θ) of impedance can be calculated from power spectra using the following approach. Let S_p be the FT of P_{fo} and S_f be the FT of $\dot{V}_{fo}$. Then we can represent these FTs in the form of their real and imaginary parts

$$S_p = A_p + jB_p \qquad \text{eqn 1.2.7}$$

and $$S_f = A_f + jB_f .$$ eqn 1.2.8

From equations 1.2.7 and 1.2.8

$$G_{pp} = S_p S_p^* = A_p^2 + B_p^2$$ eqn 1.2.9

and $$G_{fp} = S_f S_p^* = (A_f A_p + B_f B_p) + j(A_p B_f - A_f B_p)$$ eqn 1.2.10

where * indicates complex conjugate, G_{pp} is the auto-spectra of P_{fo} and G_{fp} is the cross-spectra of P_{fo} and $\dot{V}_{fo}$. A system with input x and output y can be linked by the following expression

$$H = \frac{y}{x}$$ eqn 1.2.11

where H is the system frequency response function[141]. If x is P_{fo} and y is $\dot{V}_{fo}$, then

$$H = \frac{1}{Z_{rs}} = \frac{A_f + jB_f}{A_p + jB_p} .$$ eqn 1.2.12.

After rearranging,

$$\frac{1}{Z_{rs}} = \frac{(A_f A_p + B_f B_p) + j(A_p B_f - A_f B_p)}{A_p^2 + B_p^2}$$ eqn 1.2.13.

Therefore from eqns 1.2.9 and 1.2.10

$$|Z_{rs}| = \frac{G_{pp}}{|G_{fp}|}$$ eqn 1.2.14

and $$\theta = -tan^{-1}\left(\frac{Im(G_{fp})}{Re(G_{fp})}\right)$$ eqn 1.2.15

where Im signifies the imaginary part and Re the real part.

In practice, the required auto and cross-spectra were calculated from P_{fo} and $\dot{V}_{fo}$ using the Welch method (MATLAB v6) which incorporates a Hanning window to reduce leakage[118]. These power spectra were combined as described in equations 1.2.14 and 1.2.15 above to give $|Z_{rs}|$ and θ. R_{rs} and X_{rs} were calculated from the following expressions

$$R_{rs} = |Z_{rs}| cos\theta$$ eqn 1.2.16

and $$R_{rs} = |Z_{rs}| sin\theta .$$ eqn 1.2.17

A further parameter which can be calculated from the power spectra is the coherence[118]. This is a measure of quality control which quantifies the degree of nonlinearity and extraneous noise in the system. It is calculated from the equation

$$\gamma^2 = \frac{|G_{fp}|^2}{G_{pp}G_{ff}} \qquad \text{eqn 1.2.18}$$

where γ^2 is the coherence. It is analogous to a correlation coefficient in the frequency domain and similarly ranges from 0 to 1 with the usual interpretation of these figures. It can be important in multifrequency FOT to define which frequency components are of adequate quality[142,143] but it is not essential when using a single forcing frequency as an alternative way of assessing quality control is to use the coefficient of variation[20].

The above description details how to obtain $|Z_{rs}|$ and θ from the forcing signal. To acquire these as continuous within-breath quantities requires additional refinements. If at any given time point, power spectra are calculated from P_{fo} and $\dot{V}_{fo}$ over one period or cycle of the forcing signal centred about that time point, then an impedance value can be attached to that time. If the analysis is then moved on to a later time point, a further value of Z_{rs} can be calculated and thus a time varying function generated. In one approach, the author[129] calculated a value of Z_{rs} from the data at each time point. In this situation the analysis achieves an apparent resolution of 1/(sampling frequency) although, with significant overlapping of the power spectrum windows, there is intrinsic averaging of adjacent Z_{rs} values. A second approach[132,144] is to calculate values of Z_{rs} at intervals of one period of the forcing frequency. The resolution is then reduced to 1/(forcing frequency) but each data point is independent. Here the former approach has been used. So, for example, with the 5 Hz forcing signal and sampling rate of 200 Hz, there were 40 data points per cycle of the forcing signal. Power spectra were therefore computed using 40 point windows centred on each time point to give a value of Z_{rs} for each pressure and flow sampling point. With the even number of data points in one cycle of the forcing frequency, calculation of Z_{rs} produced a 2.5 ms phase shift which was corrected before combining Z_{rs} or derived values with $\dot{V}_{br}$.

The within-breath Z_{rs} values were low pass filtered to remove biological noise using a Butterworth 8-pole filter with a cut-off frequency of 2 Hz[144]. This process employed the *filtfilt* function in Matlab which does not introduce any phase distortion. Finally the

impedance of the biological filter was subtracted from the measured total impedance to leave the subject impedance.

The detection of end-inspiratory and expiratory points required location of the points where flow changes sign. The difficulty with this was noise on the flow signal, particularly at points in the breathing waveform where there was prolonged low flow such as end-expiration. To solve this problem, noise was temporarily removed from the flow signal using a low pass Butterworth 8-pole filter with a cut-off frequency of 10 Hz. The smoothed flow was then searched for points at which flow reversed *in order of decreasing time* as flow reversals were more rapid phenomena when viewed in this direction. When a zero point was found, two actions were taken. Firstly, the exact point of zero flow closest to this time point was found by recourse to the unfiltered flow signal. Secondly, conditions were imposed which the next point of zero flow had to meet before it would be accepted. It had to be the opposite flow transition i.e. if the current point was inspiration to expiration then it had to be expiration to inspiration. It also had to lie at least 0.5 s distant from the current point. With this approach, a successful algorithm for the automatic detection of zero flow points was developed.

Volume was generated by integrating $\dot{V}_{br}$. This introduced the problem of volume drift whereby the volume seen over time shows a negative or positive trend regardless of the zeroing accuracy of the pneumotachograph. The method used to correct for this is described in Appendix 3.

The variables calculated by the above algorithm are listed in Figure 1.2.7. Their subsequent use to estimate resistive work of breathing is described in Chapter 2.1.

Elastic Work of Breathing

Theory for Non-invasive Measurement

If elastance can be assumed to be constant over the tidal volume, then elastic work of breathing is given by the following equation

$$W_{elas} = \frac{1}{2} E_{rs} V_T^{\,2} \qquad \text{eqn 1.2.18}$$

where from now E_{rs} denotes the dynamic elastance of the respiratory system. This equation gives the elastic work performed during a particular breath. It should be summed over the breaths in one minute to give it in $J.min^{-1}$ and then divided by minute ventilation to give it in $J.L^{-1}$. It can therefore be seen that a non-invasive technique for estimating E_{rs} is the basis of estimating W_{elas}.

In ventilated patients making no respiratory effort, measurement of E_{rs} is straightforward by measurement of P_{ao} and V (see Chapter 1.1). However, this is not the scenario pertaining in the pulmonary function laboratory with spontaneously breathing subjects where the activity of respiratory muscles alters airway opening pressures. The conventional approach in such subjects is to measure lung elastance using oesophageal manometry (see Chapter 1.1) but this is invasive, gives no indication of chest wall elastance and cannot be widely or routinely applied.

There have been several attempts to develop a non-invasive technique to measure elastance, both dynamic and static. The relaxation technique proposed by Rohrer in 1916[6] and repeated elsewhere[145-147] was probably the earliest. This required the subject to attain a certain lung volume (measured by spirometry) and then relax with an open glottis against a closed shutter in the breathing circuit. Pressure was measured at the mouth. This process gave one point on the pressure-volume curve for the respiratory system and was used to build up the entire curve by repeating the process at several different lung volumes. Training was required in order to perform this manoeuvre reliably and even then only 1 in 3 subjects succeeded because of failure either to maintain an open glottis or to relax completely[35]. In 1956 Heaf and Prime proposed an approach based on positive pressure breathing[33,148-151]. The subjects breathed spontaneously whilst positive pressure was introduced at the mouth which induced an increase in end-expiratory lung volume. The ratio of pressure to volume changes gave dynamic elastance. The weighted spirometer approach proposed in 1965 by Cherniack was simply a different means of applying positive airway pressure[152-155]. A final variant proposed in 1960 was to place the subject in a body plethysmograph and induce volume changes by exposure to negative pressure at the body surface[150,156-159]. A common problem with these techniques in the 1950s to 60s was the bulky apparatus required.

More recent approaches for measuring elastance non-invasively have drawn on techniques used in ventilated subjects. In the early 1980s, several studies explored a technique using constant flow inflation where elastance is given by the slope of the linear pressure-volume curve[160-163]. Some studies have attempted to use occlusion or interrupter techniques (see Chapter 1.1) which required complete subject relaxation at end-inspiration in order that change in volume and pressure can be measured[164,165] or completely passive expiration to derive a time constant[166]. Again such manoeuvres were found to require training and were not applicable to all-comers. An occlusion technique was also successfully applied during spontaneous breathing with the proportional assist mode of ventilation in intubated patients[167]. An interesting and attractive approach was the use of pressure support ventilation to abolish respiratory muscle activity and then the application of LSMLR to fit an equation of motion to the data[168,169]. Finally forced oscillometry itself can theoretically be used to estimate elastance but the technique has proved of limited practical use in this area so far[170-172]. The problem with forced oscillometry is that elastance changes markedly with frequency and inertance also becomes an increasingly significant component as frequency rises. For these reasons, the forcing frequency used must be as close to that of spontaneous breathing as possible. At such frequencies, the oscillometry measurements must be performed with the subject apnoeic as it is impossible to separate the breathing and forcing waveforms by moving average techniques.

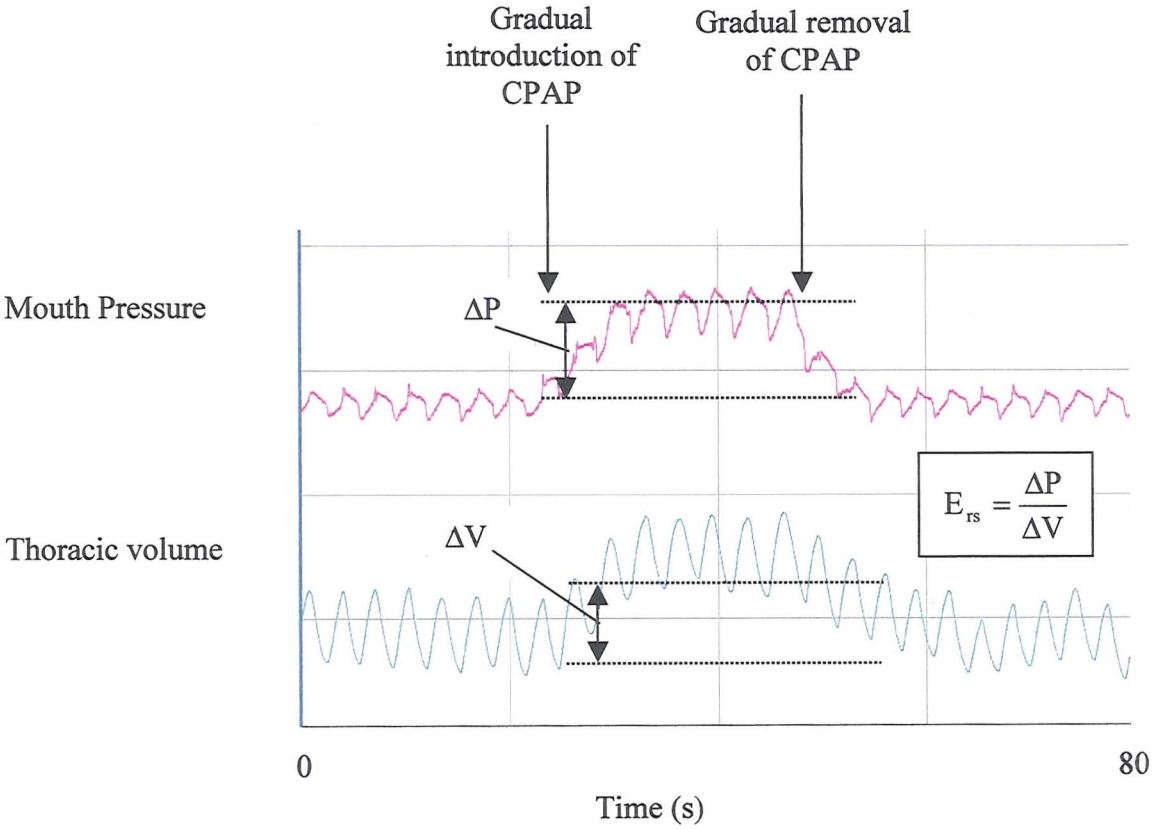
None of the techniques discussed above have achieved any mainstream acceptance for measuring elastance in the pulmonary function laboratory although several have shown promise. Two of the approaches described were chosen for further evaluation in this study, namely:-

1. **Positive pressure breathing or Continuous Positive Airways Pressure (CPAP) method**

   With the widespread availability of devices to deliver continuous positive airways pressure (CPAP) and ventilation non-invasively, the earlier problems with bulky apparatus have largely disappeared and it has now become straightforward to apply a technique based on positive pressure breathing. Since this is performed without pause during spontaneous breathing, it measures dynamic elastance. The accuracy of such an approach is affected by several assumptions. Firstly, volume change induced by positive pressure breathing is assessed at end-expiration and the method assumes relaxation or similar activity of the respiratory muscles at this time-point both with and

without CPAP. This situation is certainly not satisfied if high positive pressures are used (>2 kPa) when expiratory muscles are recruited but has been found to be the case with more modest pressures (<2 kPa)[35]. Secondly, elastance is only measured over the volume region covered by the change in end-expiratory lung volume induced and it is assumed to be constant over this region. In normal subjects this is correct for volume changes up to 80% of vital capacity[36]. In this study, CPAP of magnitude 0.8 to 1.2 kPa induced a change in thoracic volume of a similar magnitude to the tidal volume as shown in Figure 1.2.8. Elastance was estimated from the ratio of change in mouth pressure to change in thoracic volume measured at end-expiration before and after the introduction of CPAP.

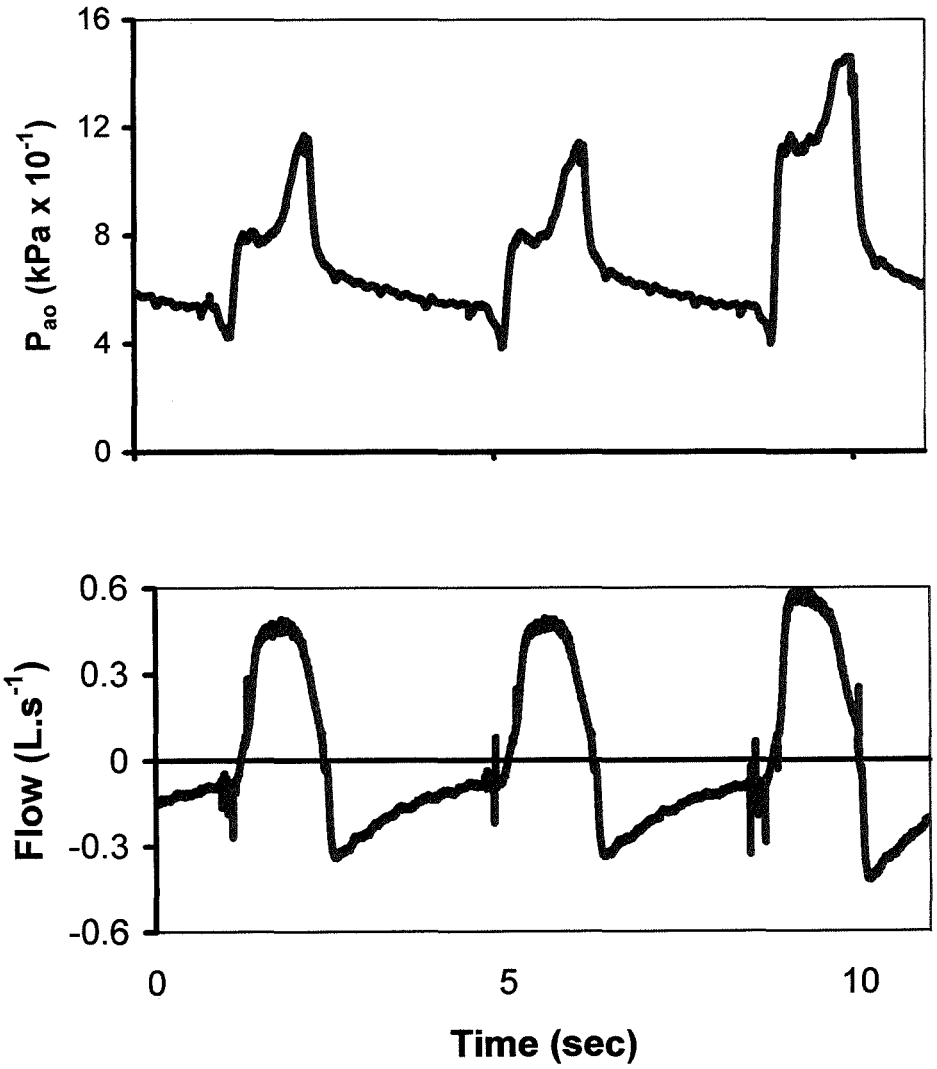
Figure 1.2.8. Effect of introduction of CPAP on mouth pressure and thoracic volume. The measurements here were from a normal subject in the pulmonary function laboratory.



2. **Non-invasive Ventilation (NIV) method**

The second method used is an approach which has only recently been proposed and employs the technique of pressure support ventilation delivered non-invasively. The subject breathes with a small amount of inspiratory pressure support delivered by a mouthpiece. After a few breaths, the inspiratory pressure is increased for one breath (typically by 0.4 kPa) (see Figure 1.2.9). E_{rs} is then estimated from the difference in P_{ao}, $\dot{V}$ and V between high and preceding low pressure breaths presuming that respiratory muscle effort has not altered between the two breaths.

Figure 1.2.9. The NIV method for estimating E_{rs}.
Inspiratory pressure support has been increased for the third breath, leading to an increase in both P_{ao} and $\dot{V}$. These measurements were taken from a ventilated subject on pressure support ventilation.



To give a value for E_{rs}, the respiratory system is assumed to follow a simple linear, two-component model, namely:-

$$P_{ao} + P_{musc} = E_{rs}V + R_{rs}\dot{V} + PEEP \qquad \text{eqn 1.2.19}$$

where

P_{musc} is the pressure generated by the respiratory muscles

PEEP is the combination of external and intrinsic PEEP.

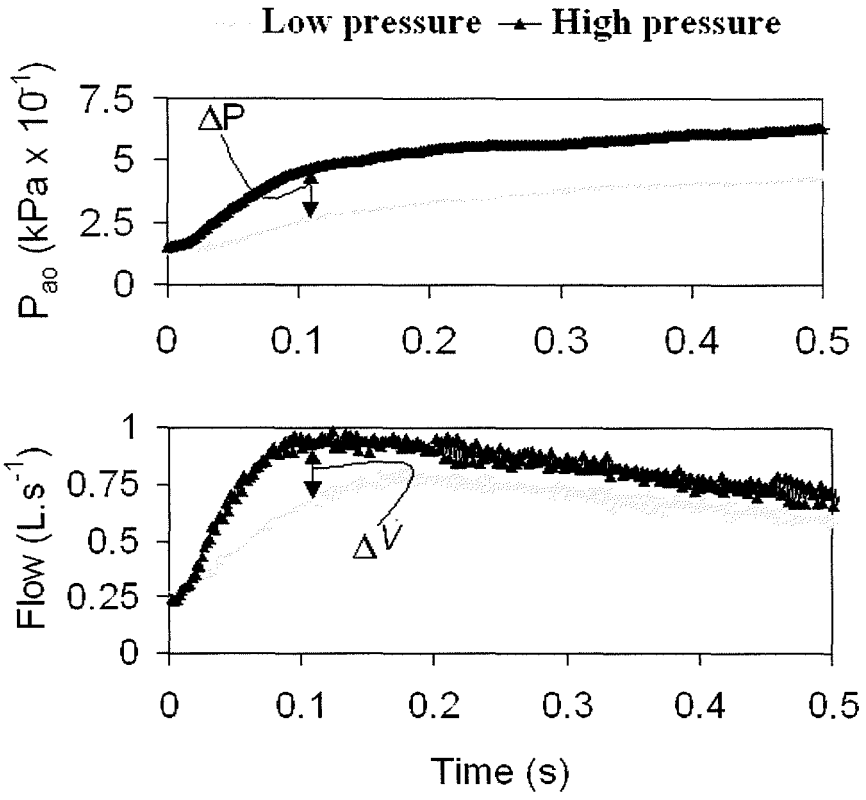
It is assumed that P_{musc} and PEEP are unchanged between consecutive breaths, then comparing high and preceding low pressure breaths, called 1 and 2 respectively,

$$\Delta P_{ao} = E_{rs}\Delta V + R_{rs}\Delta\dot{V} \qquad \text{eqn 1.2.20}$$

where $\Delta P_{ao} = P_{ao2} - P_{ao1}$ etc (see Figure 1.2.10). A set of equations (one for each sampling point) is generated by the difference between the two breaths. This represents an overdefined problem that can be solved to give an estimate of E_{rs} using LSMLR.

This method is derived from work done by Iotti[30] in which pressure support ventilation was used to abolish respiratory effort in ventilated patients and an equation of motion fitted using LSMLR. Two studies have published data using this method of differences in level of pressure support. In the first published in abstract form only[173], the method was compared with results from oesophageal manometry in 12 intubated patients. This study found it to be a method with remarkably low bias and limits of agreement for compliance (-0.00069 ± 0.001 $L.kPa^{-1}$). In the second study[172], non-invasive ventilation was delivered by facemask to 15 volunteers who were either normal (n=8) or had COPD (n=7). It was found to overestimate elastance with significant scatter in both groups (mean ± SD: 3.62 ± 0.97 $kPa.L^{-1}$ in normals and 4.86 ± 2.75 $kPa.L^{-1}$ in COPD) when compared with the rather unconventional choice of forced oscillometry as the gold standard (mean ± SD: 2.24 ± 0.51 $kPa.L^{-1}$ in normals and 4.07 ± 1.56 $kPa.L^{-1}$ in COPD).

Figure 1.2.10. Illustration of the process of aligning and subtracting corresponding points on high pressure and low pressure breaths.
P_{ao} and $\dot{V}$ are shown for the first 0.5 s of inspiration



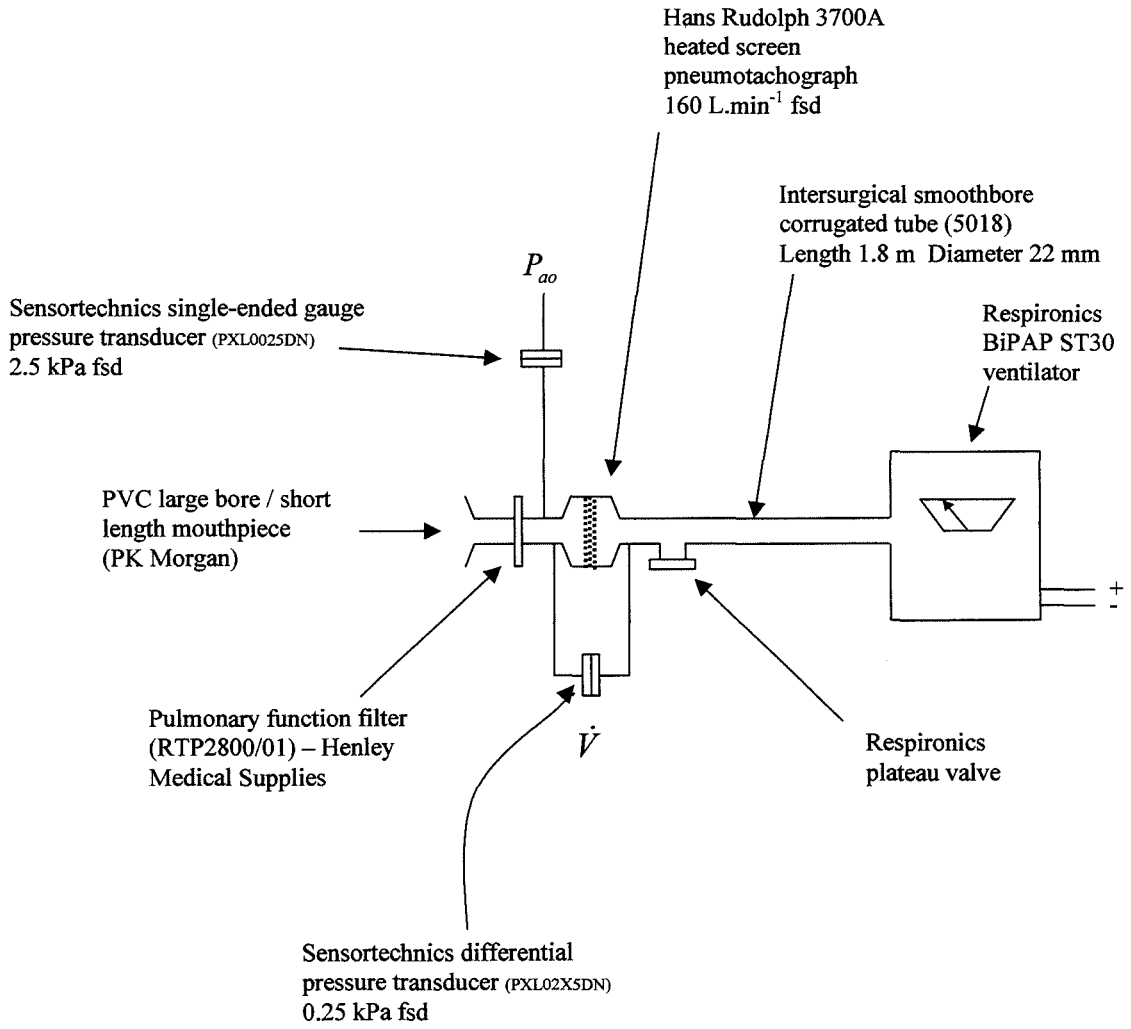
Elastic Work of Breathing: Equipment

The same equipment was used to perform the measurements for both the CPAP and NIV methods and is shown in Figure 1.2.11. The pneumotachograph and transducer for measuring mouth pressure were the ones used in the forced oscillometry measurements and were described earlier. The major change to the breathing circuit shown earlier is the replacement of the exhaust pathway for the bias flow by an exhaust valve.

In the CPAP method, the subjects were seated in a relaxed position against the chair back and were asked to breathe on a mouthpiece with nose clipped. They were told that they would be

breathing with raised pressure for approximately 20 s but were advised to breathe normally throughout. They were also asked to keep as tight a lip seal on the mouthpiece as they could comfortably maintain. After a period of 30 s of breathing with a stable volume baseline, CPAP was introduced manually up to a level of 0.8-1.2 kPa over a period of three to five seconds. This was maintained for a further five to six breaths and then gradually removed at the same rate.

Figure 1.2.11. Equipment used to make the measurements of E_{rs}.



In the NIV method, the subjects were again seated in as relaxed a position as possible and breathed into a mouthpiece with nose clipped. They were advised that they would feel a blast of air at each inspiration but simply to ignore it and breathe normally. They were warned that the pressure through the tubing would change from time to time but they should put the same

effort into every breath regardless of ventilator activity. Again they were asked to keep a tight lip seal on the mouthpiece. The ventilator was set to spontaneous mode with an inspiratory pressure of 0.6 kPa and no expiratory pressure. After 30 s, the inspiratory pressure setting was increased (manually during the expiratory phase) by 0.3-0.4 kPa. This was repeated 8 to 12 times in total in two recording periods each lasting approximately two minutes and separated by an interval of two minutes.

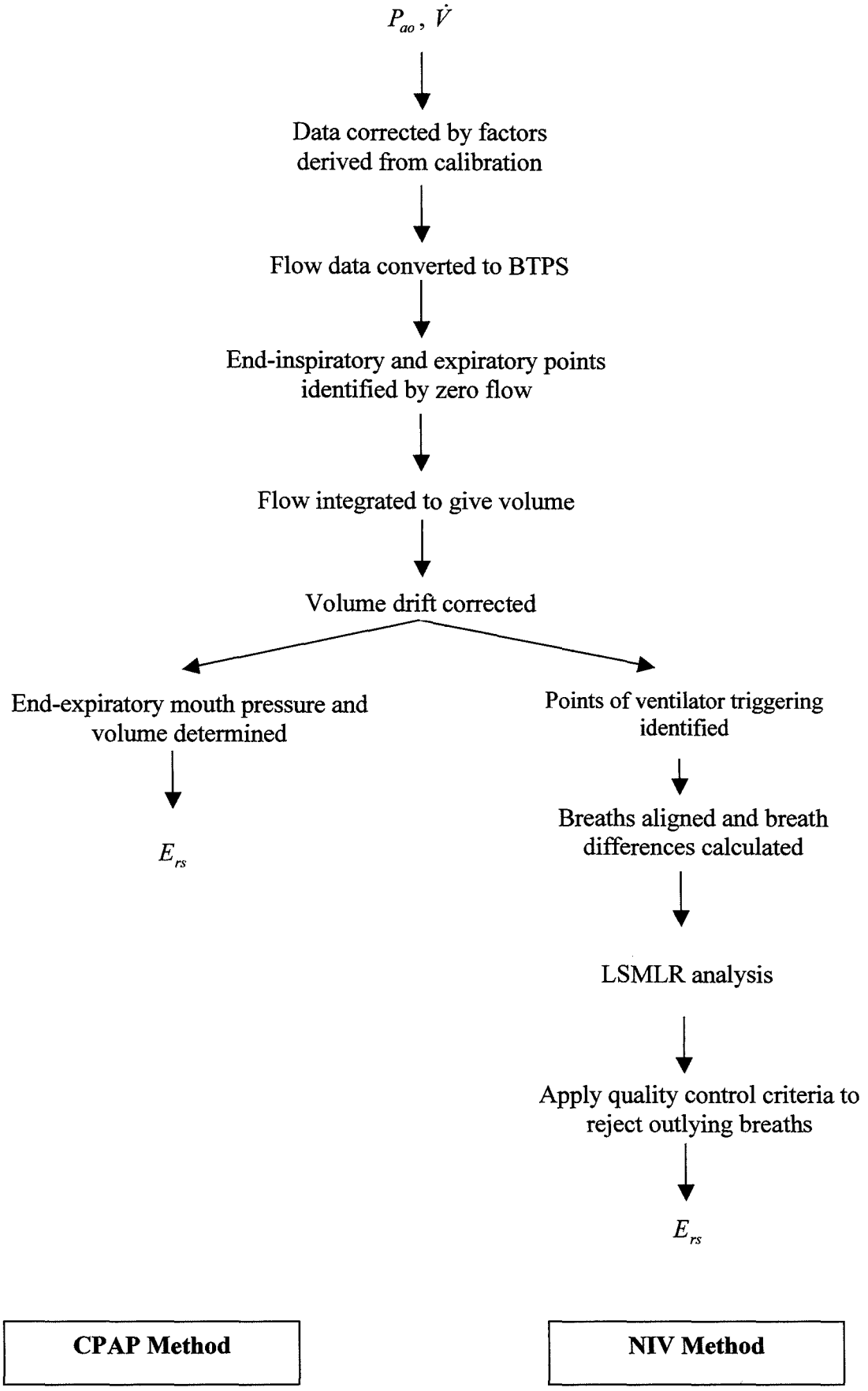
These measurements when performed on intubated subjects involved an essentially identical procedure and the equipment used is shown in Figure 1.3.1. The measurements of P_{ao} and $\dot{V}$ were performed whilst on pressure support ventilation with an inspiratory pressure of 1.0-1.2 kPa and external positive end-expiratory pressure (PEEP) of 0.5-0.7 kPa. The increments of pressure for both techniques were the same as in the laboratory.

Details of the calibration procedure, biological filtration and data acquisition system were given earlier in this Chapter. For these measurements, the analogue signals were digitised at a sampling rate of 500 Hz.

Elastic Work of Breathing: Software Algorithms

These calculations again used only P_{ao} and $\dot{V}$ data and were performed with MATLAB. The algorithms are shown in Figure 1.2.12. The first part of the algorithm was the same as for the implementation of the forced oscillometry method and was described earlier (Figure 1.2.7). The two algorithms diverged after volume drift was corrected. In the CPAP method, the only requirement thereafter was to determine the end-expiratory values of P_{ao} and V. These results were then exported to EXCEL (Microsoft Corp., USA) and inspected manually for each manoeuvre to determine that a satisfactory step in end-expiratory V could be identified. To improve accuracy, the average of three end-expiratory P_{ao} and V values were taken pre and post each step in pressure. Values during the transition in P_{ao} were not used. In addition a single elastance value was calculated from each recording by averaging the P_{ao} and V changes from the step up and step down in P_{ao}.

Figure 1.2.12. Outline of the algorithm used to analyse the CPAP and NIV results.



The NIV algorithm was more complex. To align high and low pressure breaths for subtraction, a point on the breath needed to be identified to provide a reference for alignment. One option used in earlier studies[172] was the point of zero flow. However, this was not found to be the optimum approach because, until the ventilator was triggered, the flow and pressure in high and low pressure breaths were the same (excluding biological variation). Triggering with the BiPAP ST30 (Respironics Inc., Murraysville, Pennsylvania, USA) is preset and flow-controlled and typically occurs 0.1-0.2 s into a breath. After triggering, flow and pressure in the high pressure breaths rose at a faster rate than in the low pressure breaths. The typical appearance of flow in early inspiration was therefore as shown in Figure 1.2.13. As a consequence, if the point of zero flow (Z) was used to align breaths, the first 50 to 100 points (sampling rate of 500 Hz) in the LSMLR analysis added nothing but noise to the analysis. It was more logical to attempt to align the breaths at the point at which they diverged (i.e. ventilator triggering) and start the LSMLR analysis from there. Several points were considered as candidates for automatic detection of inter-breath reference positions (Figure 1.2.13), e.g. minima in P_{ao} (MP), maxima in $d\dot{V}/dt$ (GF) or dP_{ao}/dt (GP) but the point of inflexion of flow (IF) combined the qualities of being a logical starting point and was consistently demonstrated in the traces from most subjects.

A point of inflexion simply represents a point where a curve changes direction sharply. At such a point, the rate of change of the gradient ($d^2\dot{V}/dt^2$) is a maximum. At any maximum, the derivative of the quantity is zero. Hence, at the points of inflexion in flow

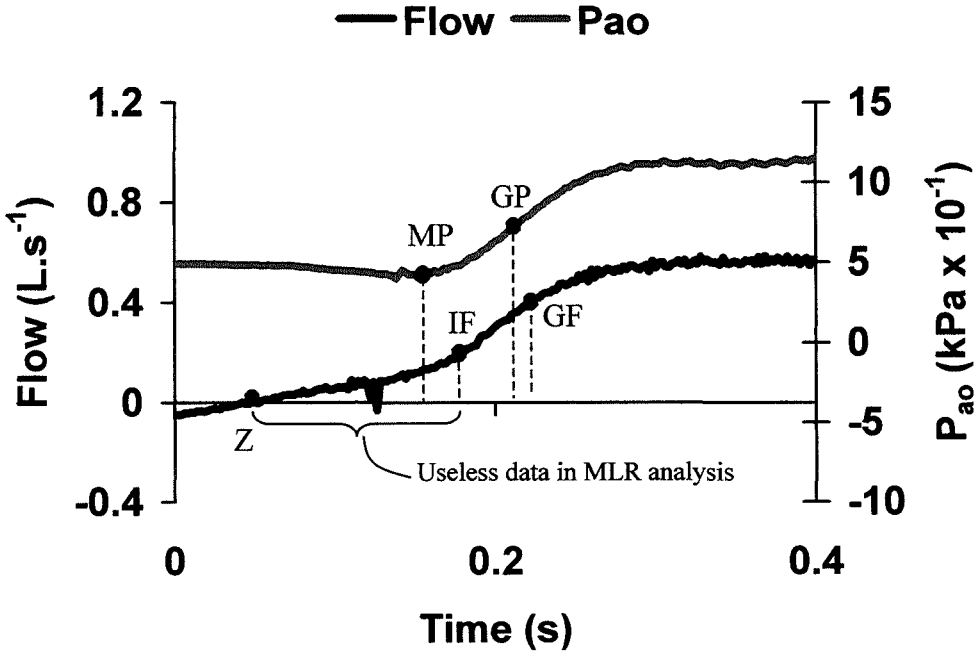
$$\frac{d^3\dot{V}}{dt^3} = 0 . \qquad \text{eqn 1.2.21}$$

The steps used by the algorithm were as follows. Firstly, the point of maximum gradient in flow following the zero flow point at the start of inspiration was located. This was generally beyond the ventilator triggering point (see Figure 1.2.13). Then the algorithm looked backwards in time to find the closest point satisfying the condition in equation 1.2.21. All these operations were sensitive to noise in the $\dot{V}$ waveform and were therefore performed on data that had been temporarily smoothed using a low pass filter (Butterwoth 8-pole cut off frequency 10Hz). Typical results are shown in Figure 1.2.14.

Having identified points of reference with which to align the high pressure breaths with preceding low pressure breaths, differences were calculated. A set of *n* equations (equation

1.2.20) were established for each low pressure breath by comparing it with the next high pressure breath. *n* is the sampling rate divided by the time interval over which the breaths were compared (typically 250). Since there were only two unknown variables (E_{rs} and R_{rs}) and only two equations are required to solve for two unknowns, this represented an overdefined problem which was solved by statistical means (LSMLR).

Figure 1.2.13. P_{ao} and $\dot{V}$ in early inspiration.
Several candidate points for the start of the LSMLR analysis are shown, namely Z – point of zero flow, MP – point of minimum in P_{ao}, IF – inflexion point in $\dot{V}$, GP – maximum gradient in P_{ao} and GF – maximum gradient in $\dot{V}$. The data wasted by using point Z as the starting point of the LSMLR analysis is indicated.



LSMLR is well described[174] and has been widely applied to respiratory problems, mostly in children[175] but also in adults[29]. It produces the optimum values for several unknown parameters by minimising the sum of the squared residuals between the predicted and measured values of the dependent variable. The calculations required can be expressed concisely if matrix arithmetic is used. Recalling the equation which we are required to solve, namely:-

$$\Delta P_{ao} = E_{rs}\Delta V + R_{rs}\Delta \dot{V} \qquad \text{eqn. 1.2.20}$$

this has become a set of n simultaneous equation for each low pressure breath. Let $\boldsymbol{Y}$ represent the $n \times 1$ vector of ΔP_{ao} values, $\boldsymbol{X}$ represent the $n \times 2$ matrix of ΔV and $\Delta \dot{V}$ values and $\boldsymbol{b}$ the 2×1 vector comprising the unknowns E_{rs} and R_{rs}. Then

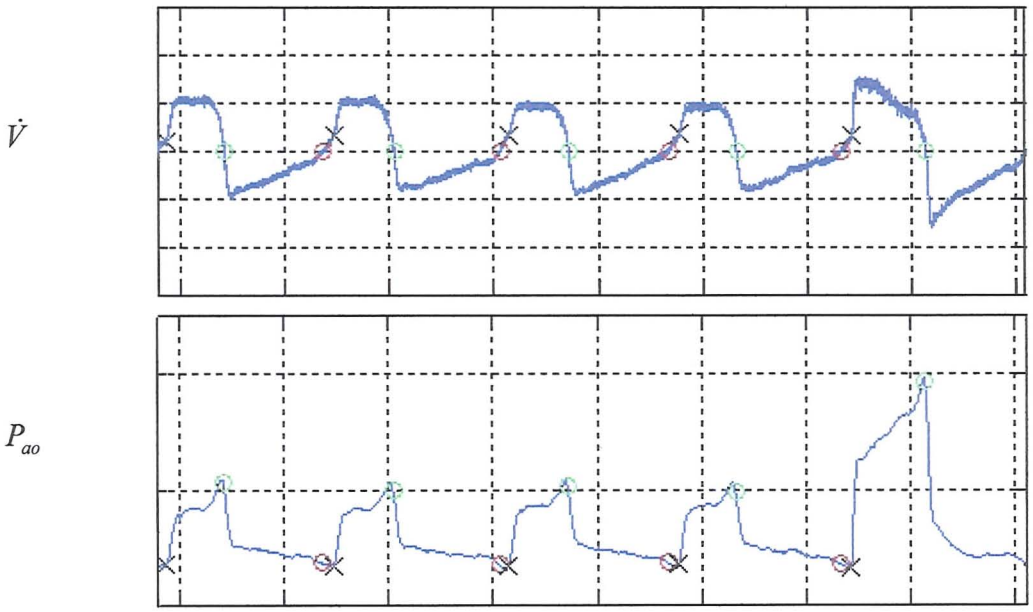
$$\boldsymbol{Y} = \boldsymbol{X}\boldsymbol{b} + \varepsilon \qquad \text{eqn 1.2.22}$$

where ε is the error. The optimum values for E_{rs} and R_{rs} are given by the equation

$$\hat{\boldsymbol{b}} = (\boldsymbol{X}^T \boldsymbol{X})^{-1} \boldsymbol{X}^T \boldsymbol{Y} \qquad \text{eqn 1.2.23}$$

where ^{T} indicates matrix transpose, $^{-1}$ matrix inverse and $\hat{\boldsymbol{b}}$ that this is a least squares estimate rather than an exact solution. The calculations involved are laborious but thankfully done by computer.

Figure 1.2.14. Automatic detection of reference points used to align breaths for subtraction.
P_{ao} and $\dot{V}$ are shown for five breaths, the last of which is a high pressure breath. o and o are points of zero flow at the beginning and end of inspiration and expiration respectively. X on the flow curve is point IF. (Measurements from a normal subject in the pulmonary function laboratory).



In applying LSMLR to the NIV data, there were two further issues which needed to be addressed. Firstly, over what time interval should a comparison be made between the high and low pressure breaths? On the one hand, this was defined by the range of validity of the assumptions used to generate the mechanical model. A major model assumption was that the

muscular effort was identical in the portion of the breath compared. This was generally seen to break down in the later stages of inspiration as the shape of the flow and pressure curves began to diverge between breaths but the location of this point in each breath was variable. On the other hand, sufficient data points needed to be included in the analysis so as to provide an accurate estimate of E_{rs} and R_{rs}. At the start of inspiration, $R_{rs}\Delta\dot{V}$ is much larger than $E_{rs}\Delta V$ and unsurprisingly it was seen that R_{rs} reached a stable value before E_{rs}. Empirically it was found that the inclusion of 0.5 s of data for comparison between breaths was an acceptable compromise between these two competing issues. This gave a set of 250 equations from which to calculate the values of E_{rs} and R_{rs}.

Secondly, quality control criteria need to be applied to the data to exclude results with a poor fit. The most commonly quoted parameter is R^2, the coefficient of determination, although several other measures of aptness of fit have been used, e.g. root mean square residual, normalised residual and standard error of coefficients. It was not possible to make use of R^2 with LSMLR as implemented here because the prediction equation was constrained to go through the origin, which made the value of R^2 uninterpretable[174]. The approach adopted was to exclude obvious outliers and then assess quality of the data by looking at the scatter of the results. Breaths were identified as outliers if they obviously violated the model assumptions, in particular the requirement that muscular effort should remain unchanged between high and low pressure breaths. The exact conditions applied were that at the end of the comparison interval (i.e. 0.5 s) the low pressure breath should have a lower pressure and flow that the high pressure breath and that its volume should be more than 0.025L smaller. This volume difference was chosen to exclude erroneously high values of elastance generated by a reduction in muscular effort.

Work against Intrinsic PEEP

Theory for Non-invasive Measurement

From Chapter 1.1, the work done against intrinsic PEEP is given by

$$W_{PEEP} = PEEP_{i,dyn}V_T \qquad \text{eqn 1.2.24}$$

It requires therefore measurement of the value of $PEEP_{i,dyn}$ which is conventionally performed as follows:-

1. **Controlled Ventilation**

   This is the simplest scenario in which to measure $PEEP_{i,dyn}$ as it can be determined directly from measurements of P_{ao} and $\dot{V}$ provided the subject makes no respiratory effort. $PEEP_{i,dyn}$ is given by the size of the change in P_{ao} at the end of expiration required to initiate inspiratory flow[176].

2. **Spontaneous Breathing**

   This requires the measurement of P_{oes} and gastric pressure (P_{gas}). $PEEP_{i,dyn}$ is measured as the abrupt drop in P_{oes} (ΔP_{oes}) occurring before flow becomes inspiratory. P_{gas} is needed to compensate for expiratory muscle activity which increases alveolar pressure. A number of methods of correction have been proposed such as subtracting the expiratory rise in P_{gas}[65] ($\Delta P_{gas,1}$) or subtracting the decrease in P_{gas} at the beginning of inspiration[64,65]. The latter can be either the complete fall ($\Delta P_{gas,2}$) or the fall from the expiratory peak in P_{gas} to the value at zero flow ($\Delta P_{gas,3}$). These methods have recently been compared with each other and with the Campbell diagram as gold standard[177,178].

An acceptable non-invasive method for measuring work against intrinsic PEEP was not found in this study. This section serves to document the approaches considered.

1. **Respiratory waveform variation (RWV)**

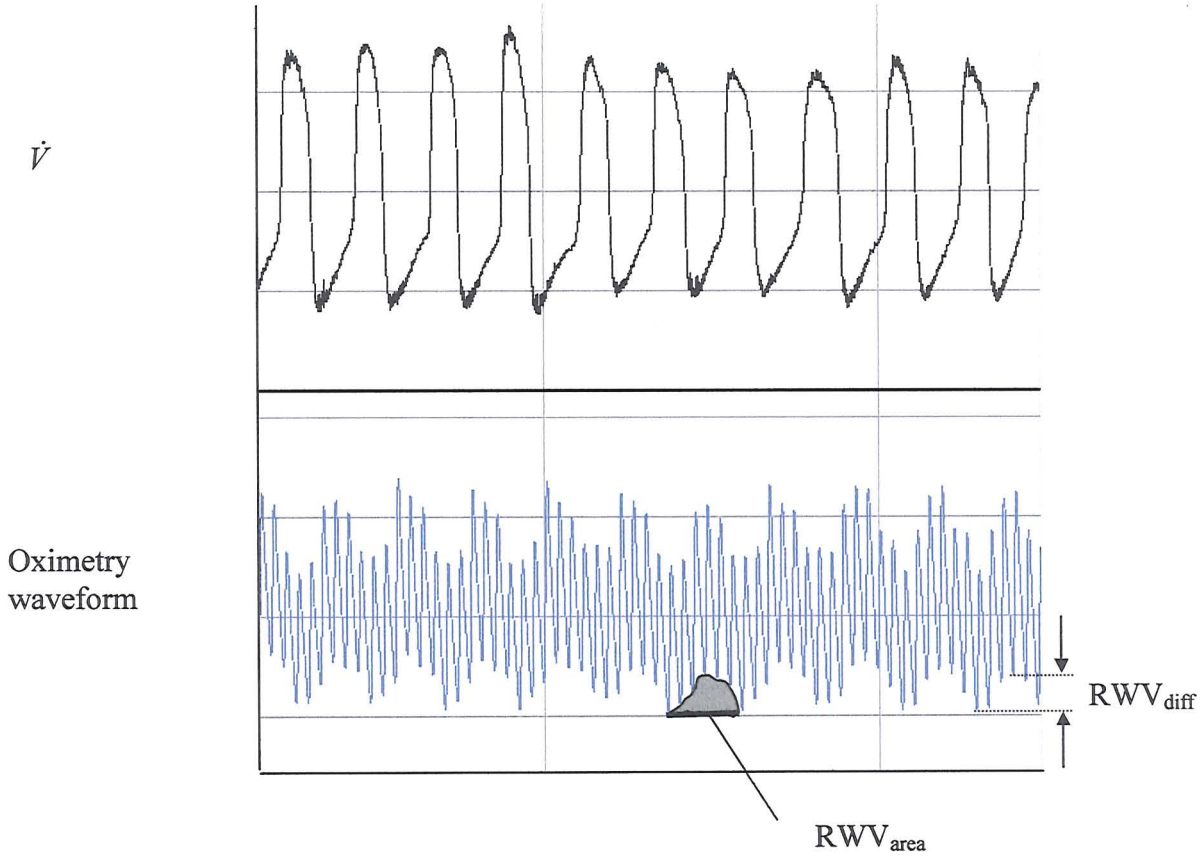
   This is a phenomenon seen in the pulse oximetry waveform in subjects with severe airways obstruction (Figure 1.2.15)[179-182]. It is thought to be due to differences in arterial blood pressure between inspiration and expiration, i.e. pulsus paradoxus, which in turn is strongly related to the degree of airways obstruction[183,184]. Since dynamic hyperinflation and $PEEP_i$ are associated with airways obstruction, it has been postulated that RWV could be a surrogate measure of $PEEP_i$. In the single study where this has been evaluated, the correlations between RWV and pulsus paradoxus and RWV and $PEEP_i$ had r^2 values of 0.88 and 0.96 respectively[182].

2. **Pulse transit time (PTT)**

   This is a parameter currently of interest in the field of obstructive sleep apnoea hypopnoea syndrome which bears a strong relationship to arterial blood pressure and is measured non-invasively. It is the time taken for the arterial pulse pressure wave to

travel from the heart to the point of measurement, such as the pulse oximeter probe on the subject's finger. It is usually measured by the time delay between the start of the R wave on the electrocardiogram (ECG) and a fixed point on the oximetry waveform (e.g. 50% of the peak height of the pulse). Changes in PTT are strongly related to changes in blood pressure (and hence would detect pulsus paradoxus)[185] (r^2=0.72) and oesophageal pressure[186] (r^2=0.88) during breathing. By analogy with the reasoning for RWV, it is therefore also possible that PTT could be a surrogate measure of $PEEP_i$. This hypothesis has not previously been tested.

Figure 1.2.15. Illustration of the phenomenon of respiratory waveform variation (RWV).
Note the pronounced swing in the pulse oximetry waveform between inspiration and expiration. The magnitude of RWV is indicated. (Measurements taken from a subject with an acute exacerbation of COPD).



Conclusions

In this chapter techniques have been proposed which allow the non-invasive estimation of the components of work of breathing. Detailed descriptions have been given of the equipment used to implement these techniques and the mathematical steps involved in calculating and interpreting the results.

1.3 Conventional Physiological Methods

Introduction

The conventional physiological techniques used in these studies are described in this chapter.

Measurements in Ventilated Patients on the Intensive Care Unit

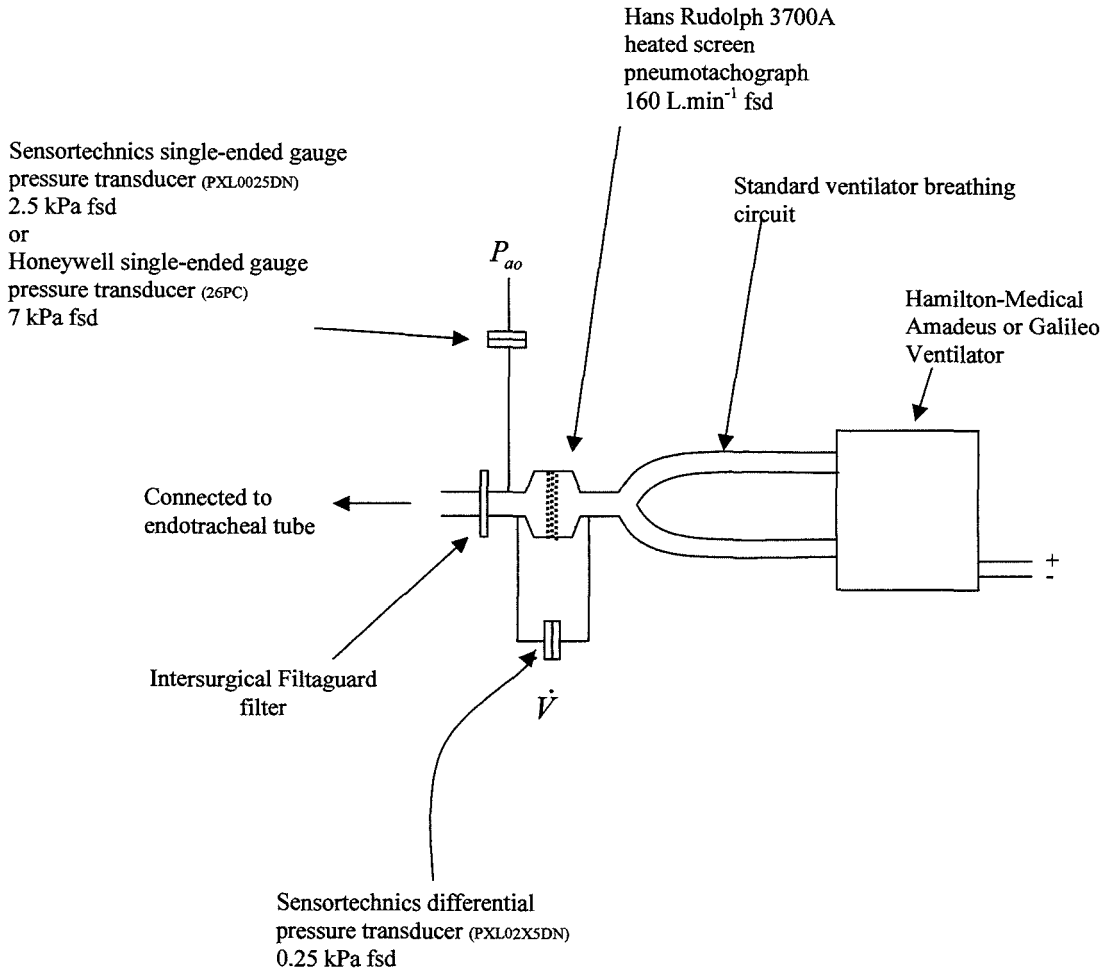
P_{ao} and $\dot{V}$ measurements were made on ventilated patients to validate the elastance techniques. The breathing circuit used is shown in Figure 1.3.1. The time delay between the P_{ao} signal measured by the two different pressure transducers was determined as described in Appendix 4 and corrected in software. The design of the FOT machine ensured that there was no time delay between P_{ao} measured by the Sensortechnics transducer and $\dot{V}$.

To calculate E_{rs} conventionally, the intubated subjects had a period of volume controlled ventilation following sedation with remifentanil (Glaxo Wellcome UK Ltd., Uxbridge, Middlesex, UK) or propofol (AstraZeneca, London, UK). The absence of muscular effort was assessed from the ventilator pressure waveform during a 5-10 second period of apnoea. Inspired oxygen concentration and PEEP were unchanged between pressure support and controlled ventilation. Measurements were taken of P_{ao} and $\dot{V}$ over a period of two to five minutes. E_{rs} was calculated for each breath by determining the points of zero flow at the beginning of inspiration (point 2) and expiration (point 1) with no end-inspiratory pause and calculating

$$E_{rs} = \frac{P_{ao2} - P_{ao1}}{V_2 - V_1} \qquad \text{eqn 1.3.1}$$

(see also Chapter 1.1). The final value was the average over all the breaths. Values were excluded from breaths where there was obvious spontaneous effort causing a dip in P_{ao}. During the period of controlled ventilation, $PEEP_{i,st}$ was also determined using the end-expiratory occlusion technique (see Chapter 1.2) via the preset function on the Galileo ventilator (Hamilton-Medical, 7403 Rhäzüns, Switzerland).

Figure 1.3.1. Breathing circuit used when measuring P_{ao} and $\dot{V}$ on ventilated patients.



Measurements in the Pulmonary Function Laboratory

Oesophageal and Gastric Manometry

P_{oes} and P_{gas} were required to calculate gold standard values of W_{res}, R_L, $E_{L,dyn}$ and $PEEP_{i,dyn}$, this technique being well described[15,16,21,187]. Latex balloons attached to PVC catheters (Ackrad Laboratories Inc., Cranford, NJ, USA) were used (Figure 1.3.2). The working range of the balloon catheter (i.e. the range over which changes in internal volume of the balloon did not influence pressure within the balloon catheter system, this remaining <0.05 kPa) was determined using the method described by Coates[188]. Figure 1.3.3 shows the pressure-volume relationship indicating that a volume of 0.5 ml was appropriate for inflating the balloon.

Figure 1.3.2. Dimensions of the oesophageal balloon catheter.

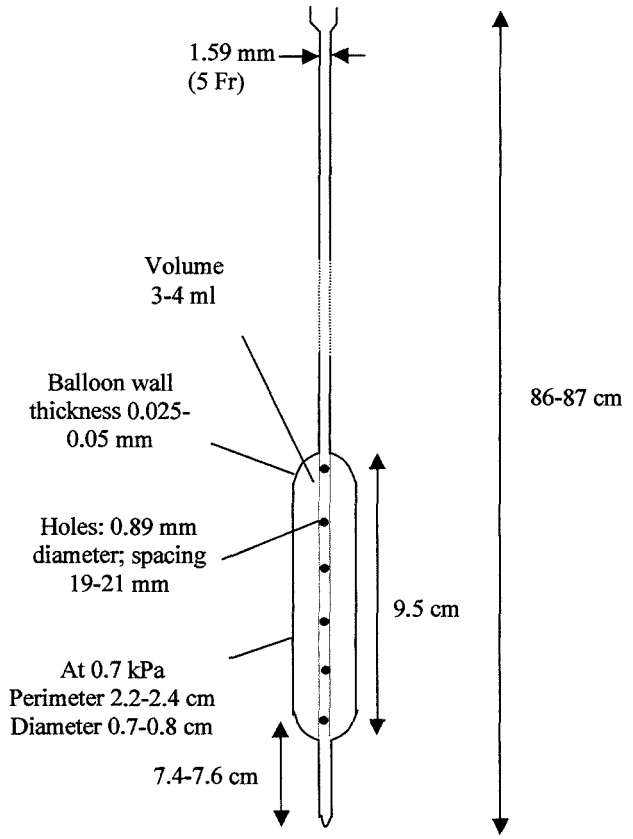
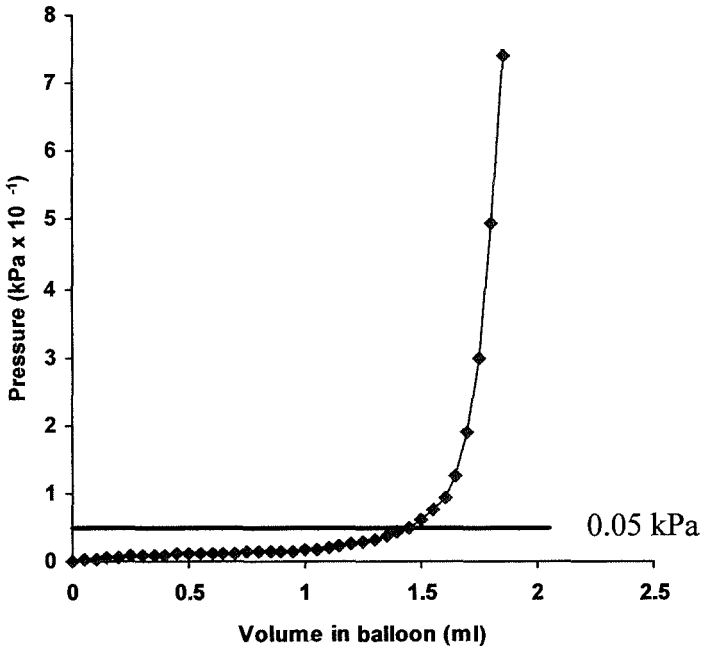
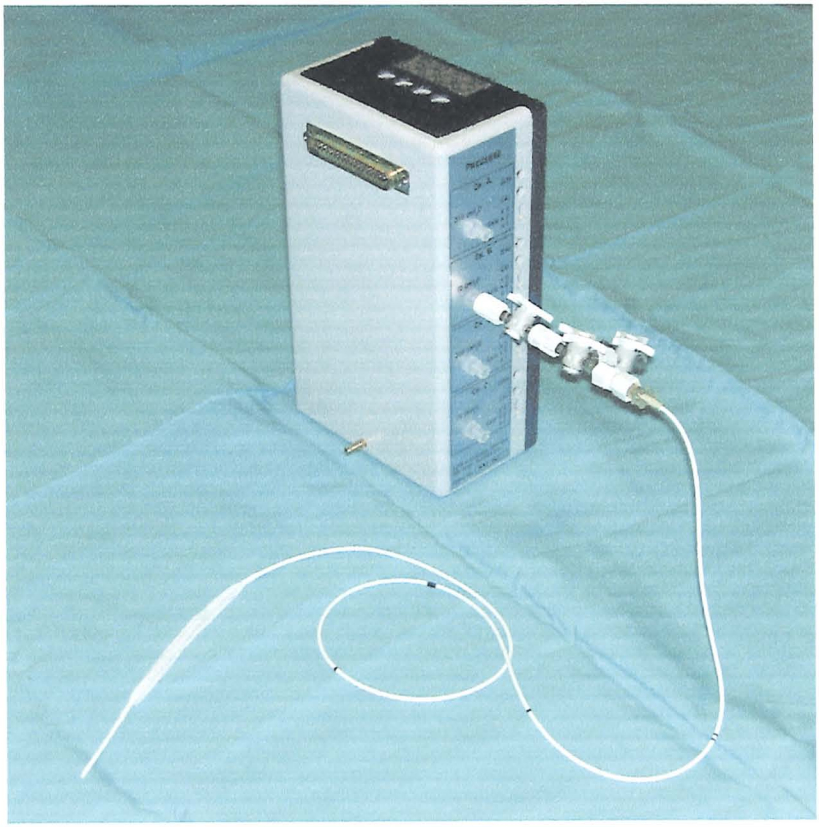


Figure 1.3.3. Working volume of the oesophageal balloon catheter.
Pressure-volume relationship of the balloon determined by the method described by Coates[188].



The balloon catheters were inserted in a conventional manner[188] using topical analgesia for the upper airway (2 ml of nebulised 4% lidocaine). Each balloon was initially inflated to 3-4 ml to remove any folding of the balloon walls. The volume in the oesophageal balloon was then reduced to its working volume of 0.5 ml whereas the volume in the gastric balloon was reduced to 2 ml[189]. The adequacy of the balloon position for measuring P_{oes} was assessed using the occlusion test[190]. Occlusion was achieved using a 3 way tap (Hans Rudolph 2100B, Hans Rudolph Inc., Kansas City, Missouri, USA) with the tap not completely closed to prevent glottis closure. Balloon position was considered to be acceptable when $0.95 < \Delta P_{ao}/\Delta P_{oes} < 1.05$ during the occlusion test. To measure P_{oes} and P_{gas}, an array of four pressure transducers (Honeywell 26PC series, Bracknell, Berkshire, UK) was custom-built (DCPB Electronics, South Glasgow University Hospital NHS Trust). This interfaced directly with the BIOPAC system (Figure 1.3.4). The pressure transducers were single ended gauge sensors, two with range ±7 kPa and two with range ±35 kPa. Only the former were used for measurement of P_{oes} and P_{gas}. Further technical specifications of the balloon catheters and the pressure transducers (including linearity, frequency response and volume coefficient of displacement) are given in Appendix 4.

Figure 1.3.4. Pressure transducer array with an oesophageal balloon catheter.



Three point calibration covering the working pressure range was performed on each day that the transducer array was used. The signals were low pass filtered at 100 Hz and the analogue signal sampled at either 200 or 500 Hz depending on the experiment being performed. Transpulmonary pressure was determined by subtracting P_{ao} (measured by the FOT transducer) from P_{oes} after correcting for transducer phase delay in software.

Values were calculated for R_L during inspiration ($R_{L,insp}$) and expiration ($R_{L,exp}$) for each breath by two techniques. Firstly, LSMLR was applied to the following model:-

$$P_{oes} - P_{ao} = P_0 + E_{L,dyn}V + R_{L,insp}\dot{V}_{insp} + R_{L,exp}\dot{V}_{exp} \qquad \text{eqn 1.3.1}$$

where P_0 is a constant and

$\dot{V}_{insp}$ and $\dot{V}_{exp}$ represent flow during inspiration and expiration respectively and were otherwise set to zero[21].

Secondly, least-squares regression was used to calculate $R_{L,insp}$ and $R_{L,exp}$ after elastic pressure changes were removed by a computational method analogous to the electrical subtraction technique of Mead and Whittenberger[15]. V was obtained by integrating $\dot{V}$ (obtained from the FOT pneumotachograph). The issues of volume drift and BTPS conversion are covered in Appendices 2 and 3.

W_{res} was calculated from the area enclosed by the loop formed by a plot of P_{oes}-P_{ao} and V. It was divided further into inspiratory and expiratory components ($W_{res,insp}$ and $W_{res,exp}$ respectively) by assuming constant lung compliance over the tidal volume and joining the points of zero flow. The calculation of $E_{L,dyn}$ from P_{oes} data is described in Chapter 1.1. Similarly, the calculation of $PEEP_{i,dyn}$ was covered in Chapter 1.2. Typical data collection periods were for one minute performed at least in duplicate.

Lung Volumes and Gas Transfer

With the exceptions of the asthmatic subjects undergoing histamine challenge tests and the subjects in the study on exacerbation of COPD, all spirometry and lung volumes were measured using a constant volume body plethysmograph (SensorMedics V6200 Autobox). The variables measured were slow or relaxed vital capacity (VC), forced vital capacity (FVC),

forced expiratory volume in one second (FEV_1), FEV_1/FVC or FEV_1/VC ratio, residual volume (RV), total lung capacity (TLC), inspiratory capacity (IC), airway resistance (R_{aw}), specific airways conductance (sG_{aw}) and peak expiratory flow (PEF)[191]. In the histamine challenge test, spirometry was performed by the subjects using a wedge bellows spirometer (Vitalograph, Maids Moreton, Buckingham, UK). The subjects in the study on exacerbation of COPD had spirometry performed using a laptop-based spirometer (KoKo Spirometer, Ferraris Respiratory, Louisville, USA). The diffusing capacity for carbon monoxide (T_{LCO}) was measured using the single breath technique (SensorMedics Vmax29 System^{TM})[192]. These values were corrected for haemoglobin concentration.

Body plethysmography and gas transfer measurements were performed by trained pulmonary function technicians. Quality control and procedures of testing followed the guidelines of the European Respiratory Society endorsed by the British Thoracic Society and the Association of Respiratory Technology and Physiology[191-193]. Results of at least three satisfactory manoeuvres were analysed and the reported values were the highest value for FEV_1, VC and FVC and the mean results for each of the remaining indices. IC was measured during the slow VC manoeuvre which was repeated until two IC values were within 10% of each other and the average of these two values was used. Predicted normal values were calculated using the European Community for Steel and Coal (ECSC) equations[191,192]. The predicted value for IC was obtained by subtracting the value for FRC from that for TLC.

Capillary Blood Sampling and Transcutaneous Oxygen/Carbon Dioxide Measurement

Capillary sampling of arterialised capillary blood was performed to obtain values for arterial partial pressure of oxygen (P_aO_2) and carbon dioxide (P_aCO_2)[194]. A nictotinate vasodilator cream (Transvasin, SSL International plc, Knutsford, UK) was applied to the earlobe and the subject sat at rest for 20 minutes. The earlobe was then punctured using a 21G gauge needle, blood was collected into a heparinised 140 μL capillary tube (Multicap, Bayer Diagnostics, Sudbury, UK) and analysed immediately on an arterial blood gas analyser (Chiron Diagnostics Rapidlab 865, Halstead, UK). The Alveolar-arterial oxygen gradient ($P_{(A-a)}O_2$) in kPa was calculated from the equation[195]:-

$$P_{(A-a)}O_2 = 0.2093(P_B - 6.3) - P_aCO_2\left(0.2093 + \frac{0.7904}{R}\right) - P_aO_2 \qquad \text{eqn 1.3.2}$$

where R was obtained from the values at contemporaneous cardiopulmonary exercise testing.

Transcutaneous oxygen and carbon dioxide partial pressure ($P_{tc}O_2$ and $P_{tc}CO_2$) were measured during exercise using a heated sensor attached to the chest wall which combined a modified Clark polarographic oxygen electrode and a modified Severinghaus solid state pH electrode for the measurement of carbon dioxide (E5280 Solid State, Tina, Radiometer A/S, Copenhagen, Denmark). The system (E5280, Radiometer, Copenhagen, Denmark) was calibrated *in vitro* at two points (the first calibration gas contained 5% carbon dioxide and 20.9% oxygen and the second 10% carbon dioxide in nitrogen) and *in vivo* after the output of the heated transcutaneous electrode was stable at 45^0C (10-20 minutes) using an earlobe specimen of arterialised capillary blood. This technique has previously been validated in Glasgow Royal Infirmary (GRI)[196,197].

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing[195,198] was performed using an electromagnetically braked cycle ergometer (Corival, Medgraphics Corp., St Paul, MN, USA) with breath-by-breath gas exchange variables and ventilation measured using a software-based system (MGC-CPX System, Medgraphics Corp., St Paul, MN, USA). Gas analysers were calibrated with certified gas mixtures, and the pneumotachograph system was calibrated using a three litre syringe before each exercise test. Pulse oximetry (Nellcor NPB-295, Pleasanton, California, U.S.A.) was used to measure heart rate (HR) and oxygen saturation (S_pO_2). The subjects were initially monitored for 2 minutes whilst seated on the cycle ergometer with a nose clip in place and breathing through the pneumotachograph. They were then instructed to cycle with no load for a further three minutes. Thereafter either an incremental or endurance exercise protocol was followed. In the **incremental** protocol, the workload was increased every minute by a constant amount ranging from 5 to 25 W. The size of the step was estimated so as to give rise to a loaded cycling time of 8 to12 minutes. Cycling continued until symptoms prevented further exercise or the pedalling rate could not be maintained above 40 revolutions per minute and the primary symptom limiting exercise was recorded. In the **endurance** protocol, the subject cycled at a constant work rate which was calculated to be a fixed

percentage (70 or 80%) of the maximum work rate achieved in a previous incremental test. Again, cycling continued until symptoms prevented further exercise or the pedalling rate could not be maintained above 40 revolutions per second. The modified Borg scale[199] was used to rate the intensity of breathlessness ($Borg_{dysp}$) and leg fatigue ($Borg_{leg}$) perceived before, every minute during and at the end of exercise. In the endurance tests of the bronchodilator reversibility study (Chapter 3.1), IC was measured each minute during loaded cycling by asking the subject to make a maximum inspiratory effort. From this, inspiratory reserve volume (IRV) and change in end-expiratory lung volume (ΔEELV) were calculated using the equations

$$IRV = IC - V_T \qquad \text{eqn 1.3.3}$$

$$\Delta EELV = IC_t - IC_0 \qquad \text{eqn 1.3.4}$$

where V_T is tidal volume, IC_0 is inspiratory capacity during rest at the start of the exercise test and IC_t is inspiratory capacity at time t during the test. In the endurance tests of the interstitial lung disease longitudinal assessment study (Chapter 3.2), $P_{tc}O_2$ and $P_{tc}CO_2$ values were recorded each minute.

The following variables were calculated breath-by-breath from expired gas analysis and ventilation measurements[198]:-

- VO_2 – Oxygen uptake ($L.min^{-1}$)
- VCO_2 - carbon dioxide output ($L.min^{-1}$)
- V_E - minute ventilation ($L.min^{-1}$)
- V_T – tidal volume (L)
- V_E/VO_2 - ventilatory equivalent for O_2
- V_E/VCO_2 - ventilatory equivalent for CO_2
- RR – respiratory rate (min^{-1})
- R – respiratory exchange ratio
- V_D/V_T – dead space to tidal volume ratio

Other output variables from exercise testing included:-

- T_{lim} - the duration of loaded cycling in the endurance test
- WR – the cycle work rate (W)
- HR – heart rate (min^{-1})
- HRR – heart rate reserve (min^{-1})

- BR – breathing reserve (min^{-1})
- AT – anaerobic threshold
- O_2 pulse – oxygen pulse ($ml.beat^{-1}$)
- $\Delta P_{tc}O_{2,peak}$, $\Delta P_{tc}CO_{2,peak}$ – change in $P_{tc}O_2$ and $P_{tc}CO_2$ between resting state and peak exercise (kPa)
- $P_{(A-tc)}O_2$ – Alveolar-arterial pressure gradient (kPa) calculated using $P_{tc}O_2$ and $P_{tc}CO_2$
- $_{,rest}$ – subscript indicating measurement at rest
- $_{,iso}$ – subscript indicating measurement at isotime
- $_{,peak}$ – subscript indicating peak measurement
- $_{,end}$ – subscript indicating end-exercise measurement.

Breath-by-breath values were averaged over eight breaths. The peak value was the maximum of these over the last eight breaths during loaded cycling in the incremental cycle test. The end value was the average over the last eight breaths during loaded cycling in the endurance cycle test. The isotime point was defined separately for each patient as the minimum of the two endurance exercise times rounded to the whole minute below. The dead space of the mouthpiece, pneumotachograph and valve box were known and corrected for in software. Following convention, V_E and V_T were converted to BTPS whereas VO_2 and VCO_2 were standardised to standard temperature and pressure dry (STPD). The equation used for predicted peak VO_2 was from Jones[195]. The predicted value for HR was 220-Age (years) and for maximum voluntary ventilation (MVV) was FEV_1 multiplied by 40[198]. Derived values such as HRR, BR, R, V_D/V_T, V_E/VO_2, V_E/VCO_2, O_2 pulse and $\Delta VO_2/\Delta WR$ were calculated as described in Jones[195] and Wasserman[198].

Quality of Life and Symptom Questionnaires

A number of questionnaires for measuring symptoms and health-related quality of life (HRQOL) were used in these studies. The symptom scales were completed by the investigator interviewing the subject whereas the HRQOL questionnaires were self-completed.

St George's Respiratory Questionnaire

The St George's Respiratory Questionnaire (SGRQ) is a disease specific instrument for measuring HRQOL which has been developed for and extensively used in patients with airways obstruction[200,201] and bronchiectasis[202]. It provides a Total score and three component scores: Symptoms (distress caused by respiratory symptoms), Activity (physical activities that cause or are limited by breathlessness), and Impacts (social and psychological effects of the disease). Each score can range from 0 to 100 where 0 indicates best and 100 indicates worst health. An EXCEL worksheet was used to calculate the SGRQ component scores using the method described in the User Manual and missing values were dealt with in the recommended way. Mean (95% confidence intervals) SGRQ scores in normal individuals with no history of respiratory disease are Symptoms – 12 (9-15), Activity 9 (7-12), Impacts 2 (1-3) and Total 6 (5-7)[203]. Scores in individuals with airways obstruction weakly correlate with the FEV_1. In a study where the baseline FEV_1 score was 45% predicted, the Total SGRQ score was 52[201]. A change in the Total score of four units is thought to indicate a clinically significant change in the patient[201,204].

Short Form 36

The Short Form-36 (SF-36) is a brief instrument for measuring generic HRQOL[205]. The questionnaire consists of 36 questions that cover eight health scales: physical functioning, physical role, pain index, general health, vitality, social functioning, emotional role and mental health. These eight scores can be further condensed into two items, physical and mental component scores (PCS, MCS)[206]. The scores of the eight health scales could range from 0 (the worst possible condition) to 100 (the best possible condition) and values for the general US population from 1998 are shown in Table 1.3.1[206]. PCS and MCS values are transformed to a norm-based system using values for the healthy population such that the mean score is 50 and the standard deviation 10. Again a lower score indicates worse health. The questionnaires were scored using an EXCEL spreadsheet incorporating the scoring algorithms described in the SF-36 manuals[206,207].

Table 1.3.1. SF-36 health scale scores from the US general population in 1998.

SF-36 Scale	Mean Score (SD)
Physical functioning	82.97 (23.84)
Physical role	77.93 (35.35)
Bodily pain	70.23 (23.35)
General health	70.10 (21.36)
Vitality	57.00 (21.13)
Social functioning	83.56 (23.03)
Emotional role	83.10 (31.64)
Mental health	75.22 (17.61)

The London Chest Activity of Daily Living Scale

The London Chest Activity of Daily Living Scale (LCADL) is a 15-item questionnaire designed to measure dyspnoea during activities of daily living in patients with COPD[208,209]. It consists of four components: Self-care, Domestic, Physical and Leisure. For each of the 15 items, patients score from 0: "I wouldn't do anyway", to 5 "Someone else does this for me (or helps)", with higher scores representing maximal disability.

Borg Scale

The modified Borg scale is used to rate the perceived intensity of breathlessness and leg fatigue and can be used during rest or exercise[199]. In this scale, simple verbal expressions are linked to numbers from 0 to 10, 0 being no appreciable breathlessness or leg fatigue and 10 being the maximum. The modified version is a ratio scale, i.e. a doubling of the numeric value indicates a doubling of the perceived breathlessness or leg effort.

Oxygen Cost Diagram

The Oxygen Cost Diagram (OCD) is a visual analogue scale based on a 10 cm line where daily activities (such as "brisk walking uphill", "medium walking on the level", "bed making", "standing") are ranked along the line in proportion to their associated oxygen cost[210]. The line is marked at the point above which a task would have to be stopped because of breathlessness and increasing distance along the line from 0 to 1 represents increasing exercise capacity.

Baseline and Transitional Dyspnoea Index

The Baseline Dyspnoea Index (BDI) grades dyspnoea by combining the scores in three different categories: functional impairment, magnitude of task, and magnitude of effort[211]. Dyspnoea is graded from 0 (severe) to 4 (unimpaired) for each category. The ratings for the three categories are added to form the baseline score, ranging from 0 to 12. The Transitional Dyspnoea Index (TDI) compares the patient's current dyspnoea with the baseline state with seven grades for each of the three categories. Scores range from –3 (major deterioration) to 0 (unchanged) to +3 (major improvement). The ratings on each of the three scores are added to form a total score ranging from –9 to +9.

Medical Research Council Dyspnoea Scale

The Medical Research Council (MRC) dyspnoea scale[212] is a questionnaire that consists of five statements about perceived breathlessness ranging from grade 1 ("I only get breathless with strenuous exercise") to grade 5 ("I am too breathless to leave the house").

Dyspnoea Scale from the Clinical, Radiographic and Physiologic Scoring System

The dyspnoea scale from the Clinical, Radiographic and Physiologic Scoring System for pulmonary fibrosis[213] (CRP dyspnoea scale) is a scale with 11 statements about dyspnoea ranging from "None (or same as peers) even after 30 min of vigorous activity such as

running" to "At rest". The subject is asked to choose one statement which applies to them and the scale is scored from 0 ("None") to 20 ("At Rest") respectively in steps of 2.

Visual Analogue Scales for Symptoms

The symptom scores are visual analogue scales (VAS) adapted from the study by Davies[214]. They ask about three symptoms: Quality of sleep, Wheeze and Mobility. The scale ranges from –100 ("much worse than usual") through 0 ("usual") to +100 ("much better than usual") and the subjects were asked to rate how they had felt with respect to each symptom over the previous 24 hours. The visual analogue scale for breathlessness is a similar scale ranging from –100 ("very, very much worse") through 0 ("before treatment") to +100 ("very, very much better") and the subjects were asked to rate their breathlessness at the present moment compared with that at presentation.

Paggiaro Symptom Scores

The symptom scores from the study by Paggiaro[215] rate cough, breathlessness and sputum volume and colour. Several statements are attached to each symptom and the subjects were asked to choose the most appropriate answer.

Ethical Approval

Ethical approval for these studies was obtained from the Local Research & Ethics Committee of GRI (Glasgow, UK).

Part 2: Validation of non-invasive techniques for measuring work of breathing

This section describes two studies performed to validate the techniques described in Chapter 1.2. In Chapter 2.1, the performance of forced oscillometry variables for measuring W_{res} are assessed. In Chapter 2.2, two techniques for non-invasive estimation of E_{rs} are evaluated.

Work validating the non-invasive measurement of intrinsic PEEP is not presented because very limited data were ultimately available for this purpose. RWV was absent in the intubated subjects on controlled ventilation and so no data were available from these subjects. $PEEP_{i,dyn}$ measurements were available from twelve patients with airways obstruction in the pulmonary function laboratory. However the median level of $PEEP_{i,dyn}$ was only 0.148 kPa with a range of 0.013 to 0.556 kPa. In these subjects there was no association between RWV measurements and $PEEP_{i,dyn}$. There was a significant correlation between $PEEP_{i,dyn}$ and ΔPTT_{ave} ($r=0.73$). Despite the absence of proper validation, the phenomena of respiratory waveform variation and pulse transit time were analysed further in the evaluation studies in Section 3 as these two variables are surrogate markers of respiratory effort (due to their relationship with P_{oes}) and hence might still give useful information in this respect.

2.1 The use of forced oscillometry to estimate transpulmonary resistance and resistive work of breathing

Introduction

Forced oscillometry is a method of measuring R_{rs} which is passive, requiring only tidal breathing from the subject, and can give a continuous value of R_{rs}, delineating within-breath changes with sub-second resolution. It has two main limitations. Firstly, as distal airways obstruction increases, there is worsening agreement of R_{rs} with R_L measured by oesophageal manometry[4]. Under these conditions, R_{rs} is an underestimate because of the increasing contribution of the upper airway wall, which acts as an impedance in parallel (or shunt) with the lower airway. Secondly, it is less useful for diagnosis as any pathology produces a similar pattern of abnormality in oscillometry results although differing in degree[20]. Despite these drawbacks, oscillometry performs similarly to standard tests in areas dependent on assessing airways obstruction such as bronchodilator reversibility[216] and bronchial challenge testing[217].

There has been interest of late in using less conventional oscillometry parameters to overcome the limitations of the technique or to extract added value from the measurements. A recent proposal was the use of changes in admittance (the reciprocal of impedance)[120] during bronchoprovocation. Theoretically the effect of upper airway wall shunt should be removed during calculation of the change in admittance and the results from standard oscillometry equipment compared with the head plethysmograph, although not identical, did support this claim. However, admittance could only be used to predict changes in resistance rather than absolute value. A further suggestion was the use of expiratory reactance ($X_{rs,exp}$) to demonstrate the presence of expiratory flow limitation[218]. This study showed that in COPD subjects a within-breath $X_{rs,exp}$ value below a threshold (< -0.7 kPa.s.L^{-1}) could detect expiratory flow limitation proven by oesophageal manometry with 100% sensitivity. It had also been noted in earlier work that X_{rs} decreased (becomes more negative) as airways obstruction increased and in several studies this variable appeared to correlate more strongly with FEV_1 and R_{aw} than did R_{rs}[219-221].

Aims

1. To assess the ability of R_{rs} measured by within-breath oscillometry at a single excitation frequency of 5 Hz to estimate R_L.
2. To explore the potential for using other within-breath oscillometry parameters such as X_{rs} or Z_{rs} as a surrogate measure of R_L.
3. To assess the ability of forced oscillometry measurements to predict resistive work of breathing (W_{res}) using whichever variable proved optimal.

Methods

Study Design

Oscillometry and oesophageal manometry were performed simultaneously on eleven asthmatic patients at several points during a histamine challenge test. The data generated from the first five asthmatics were used to investigate the relationship between R_L and the oscillometry variables. A linear model to predict the absolute value of R_L was generated from the data using the single most strongly correlated oscillometry variable. Then data from the remaining six asthmatics were used to assess the fit of the predictive model. Finally, single point measurements were performed in both normal subjects and others with a range of respiratory conditions (COPD, interstitial lung disease (ILD), chest wall disease and respiratory muscle myopathy) to see whether this behaviour was also seen outside the context of asthma.

Subjects

The normal and asthmatic subjects were drawn from the staff of the Departments of Respiratory Medicine and Anaesthesia at GRI. The first five asthmatic subjects had median (range) age 39 (28 - 47) years, median (range) FEV_1 of 92 (78 - 106) % predicted and median (range) FEV_1/FVC ratio of 70 (62 - 76) % and the second six median (range) age of 33 (28 -

36) years, median (range) FEV_1 of 94 (69 - 112) % predicted and median (range) FEV_1/FVC of 72 (69 - 82) %. All were non-smoking males who satisfied the BTS definition of asthma[222]. The remaining subjects were volunteers from the respiratory outpatient clinics (see Table 2.1.1). The subjects with COPD satisfied the BTS definition for this condition[223]. All the subjects with ILD had CT scan evidence of diffuse parenchymal lung disease and five were biopsy proven. The subjects with chest wall disease and myopathy used chronic nocturnal non-invasive ventilation for these conditions.

Table 2.1.1. Characteristics of the non-asthmatic subjects studied.

	Number	Age (years)	FEV_1 (% pred)	FVC (% pred)	FEV_1/FVC (%)
Normal	7 (5 male)	27 (20-30)	97 (89-107)	98 (92 –108)	83 (79-88)
COPD	9 (8 male)	68 (53-73)	54 (31-107)	104 (70-160)	39 (25-52)
Myopathy‡	2 (no males)	62 (60-64)	63 (46-79)	68 (43-93)	81 (72-90)
ILD§	9 (4 male)	61 (50-75)	84 (50-122)	105 (50-130)	77 (59-80)
Chest wall disease¶	8 (3 male)	68 (49-78)	32 (27-40)	40 (31-66)	58 (39-92)

All values are median (range)

‡Mitochondrial myopathy (1), diaphragmatic palsy (1)

§Idiopathic pulmonary fibrosis (3), connective tissue disease (3), sarcoidosis (1), silicosis (1), hypersensitivity pneumonitis (1)

¶Kyphoscoliosis (4), thoracoplasty (3), pneumonectomy (1)

Histamine Challenge Test

This followed the method outlined by Sterk[224]. Baseline spirometry, oesophageal manometry and forced oscillometry were performed. After diluent (0.9% sterile sodium chloride), histamine (Tayside Pharmaceuticals, Dundee, UK) was delivered in doubling concentrations using a jet nebuliser (Micro-Neb Nebuliser, Lifecare Hospital Supplies, Market Harborough, UK) driven by an airflow of 8 $L.min^{-1}$ (Aquilon Nebuliser System, AFP Medical, Rugby, UK) through a face mask (Duo Mask Adult, Lifecare Hospital Supplies) and inhaled for two minutes of tidal breathing with the nose clipped. The starting concentration of histamine

varied between 0.0625 $mg.ml^{-1}$ and 0.5 $mg.ml^{-1}$. Between doses of histamine, two simultaneous recordings, each of one minute's duration, were made of oesophageal manometry and forced oscillometry. The test was stopped when FEV_1 dropped to less than 60% of baseline or at a maximum concentration of histamine of 16 $mg.ml^{-1}$.

Oesophageal Manometry

This technique is described in Chapter 1.3. Values were calculated for R_L during inspiration ($R_{L,insp}$) and expiration ($R_{L,exp}$) for each breath. For the asthmatic subjects, LSMLR was used to calculate $R_{L,insp}$ and $R_{L,exp}$. The fit achieved by the LSMLR model to transpulmonary pressure values was reasonable. The median (inter-quartile range) R^2 value generated by the LSMLR analysis was 0.94 (0.89-0.97). For the non-asthmatic subjects least-squares regression was applied after elastic pressure changes were removed by the Mead-Whittenberger technique. The latter method was used in non-asthmatic subjects as occasionally in this group LSMLR produced non-physiological values of elastance and resistance. WOB_{res} was calculated from the area enclosed by the loop formed by a plot of P_{oes}-P_{ao} and V, which is equivalent to calculating the integral:-

$$WOB_{res} = \int (P_{oes} - P_{ao})\dot{V}dt \qquad \text{eqn 2.1.1}$$

and divided into inspiratory and expiratory components ($WOB_{res,insp}$ and $WOB_{res,exp}$ respectively) by a line joining the points of zero flow. These measurements were summed over the breaths for one minute and divided by minute ventilation to give results as $J.L^{-1}$. Data were excluded for breaths corrupted by swallowing artefacts and each result was the average from the breaths over one minute.

Forced Oscillometry

This technique is described in Chapter 1.2. The R_{rs} and X_{rs} values were averaged over the inspiratory and expiratory phases of each breath to give separate values for the two phases of the respiratory cycle ($R_{rs,insp}$, $R_{rs,exp}$) (see Figure 2.1.1). The values from a one-minute recording were then averaged. Following the reasoning laid out in Chapter 1.2 for estimating

WOB_{res} from oscillometry variables, integrals were calculated which combined $\dot{V}$ and the oscillometry variables R_{rs}, X_{rs} and $|Z_{rs}|$ (where the latter is the magnitude of the complex variable representing impedance) as follows:-

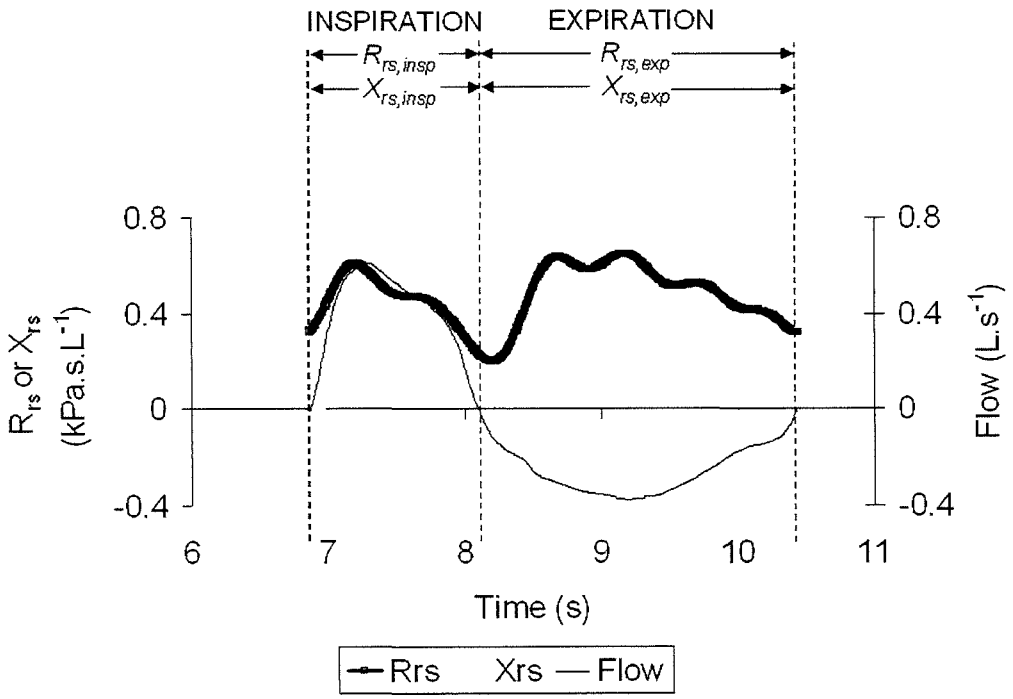
$$WOB_{FOT,R} = \int \dot{V}^2 R_{rs} dt \qquad \text{eqn 2.1.2}$$

$$WOB_{FOT,X} = \int \dot{V}^2 X_{rs} dt \qquad \text{eqn 2.1.3}$$

$$WOB_{FOT,Z} = \int \dot{V}^2 |Z_{rs}| dt \qquad \text{eqn 2.1.4}$$

Again these were calculated for each breath, separated into inspiratory and expiratory components (e.g. $WOB_{FOT,Rinsp}$, $WOB_{FOT,Rexp}$, etc.), summed over the breaths of one minute and normalised by minute ventilation.

Figure 2.1.1. Within-breath R_{rs} and X_{rs} values are shown for one respiratory cycle from one of the asthmatic subjects at the midpoint of the histamine challenge test.
$R_{rs,insp}$ and $X_{rs,insp}$ were calculated for each breath by averaging the inspiratory values for these variables. $R_{rs,exp}$ and $X_{rs,exp}$ were similarly obtained from the expiratory values.



Sample Size

An estimate of sample size was obtained by requiring the 95% confidence intervals of the bias to be ±0.025 $J.L^{-1}$. Assuming a typical value for WOB_{res} of 0.5 $J.L^{-1}$ and a pessimistic value for coefficient of variation of 18% (which was twice that for R_{rs} found in a pilot study), then the number required to give this precision on the bias was 52[225]. This leads automatically to the precision of the limits of agreement which was ±0.043 $J.L^{-1}$.

Statistical Analysis

Statistical analyses were performed with StatView v 5.0.1 (SAS Institute Inc., Cary, NC, USA). Correlation was assessed using Pearson's *r* correlation coefficients. Prediction equations were generated by least squares linear regression. Agreement of the prediction models with the absolute values was assessed using an analysis similar to that proposed by Bland and Altman[225] (indicated as "Bland-Altman"). The repeatability of measurements was calculated as a coefficient of variation by expressing the standard deviation of repeated measurements as a percentage of the mean. Median and range were used for baseline pulmonary function data.

Results

First Set of Asthmatic Subjects

Bronchoprovocation tests on the first five asthmatics produced 96 measurements. $R_{rs,insp}$ progressively underestimated $R_{L,insp}$ as airway obstruction increased (Figure 2.1.2(a)) leading to a divergence of the curve on the scatter plot from a straight line. The size of the error due to upper airway wall shunt was variable causing the scatter plot to fan out at high values. A similar relationship was seen between $WOB_{FOT,Rinsp}$ and $WOB_{res,insp}$ (Figure 2.1.2(b)). The oscillometry parameter most strongly correlated with $R_{L,insp}$ was $X_{rs,insp}$ and with $WOB_{res,insp}$ was $WOB_{FOT,Xinsp}$ (Table 2.1.2). The strength of these associations was particularly striking, illustrated in Figure 2.1.3. A tight linear relationship was preserved until the highest observed

values of $X_{rs,insp}$. Prediction equations for $R_{L,insp}$ and $WOB_{res,insp}$ were therefore derived from $X_{rs,insp}$ values.

Second Set of Asthmatic Subjects

Bronchoprovocation testing on the second set of asthmatics lead to a further 123 data points. R_L values in this group ranged from 0.0005 to 4.57 kPa.s.L^{-1} with a median value of 0.21 kPa.s.L^{-1}. The values were skewed towards the normal range because the airways of the six subjects were unconstricted except for a few points towards the end of each histamine challenge test. The lower limit of the range measured is physically unrealistic and a consequence of the significant error involved in measuring normal values of R_L by oesophageal manometry.

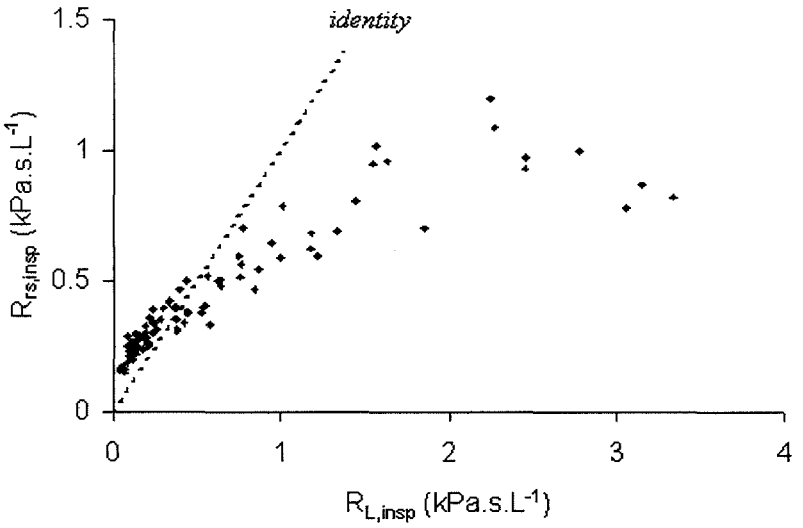
The accuracy of the equation for predicting $R_{L,insp}$ from $X_{rs,insp}$ was tested on these data and the results are shown in Figure 2.1.4(a). The equivalent results using absolute $R_{rs,insp}$ values are shown for comparison. The prediction model using $X_{rs,insp}$ is clearly more accurate at predicting $R_{L,insp}$. In particular agreement is maintained until a relatively high value of $R_{L,insp}$ (approximately 2.5 kPa.s.L^{-1}). The same analysis is repeated comparing $WOB_{FOT,Xinsp}$ and $WOB_{FOT,Rinsp}$ with $WOB_{res,insp}$ and is shown in Figure 2.1.4(b).

Non-asthmatic Subjects

Measurements were then performed on subjects with respiratory conditions other than asthma. A pair of duplicate readings was obtained for each of these subjects and the relationship between $R_{L,insp}$ and $X_{rs,insp}$ and $WOB_{res,insp}$ and $WOB_{FOT,Xinsp}$ compared as before (see Figure 2.1.5). Although scatter was greater, the results can be seen to follow largely the same linear relationship seen in the pure asthmatics. In the non-asthmatic subjects the mean (±SD) difference between the actual $R_{L,insp}$ values and that predicted from $X_{rs,insp}$ was 0.033 (±0.36) kPa.s.L^{-1}. Similarly the mean (±SD) difference between the actual $WOB_{res,insp}$ values and that predicted from $WOB_{FOT,Xinsp}$ was 0.038 (±0.16) J.L^{-1}

Figure 2.1.2. Data from the first five asthmatic subjects showing (a) $R_{rs,insp}$ plotted against $R_{L,insp}$ and (b) $WOB_{FOT,Rinsp}$ plotted against $WOB_{res,insp}$.

A



B

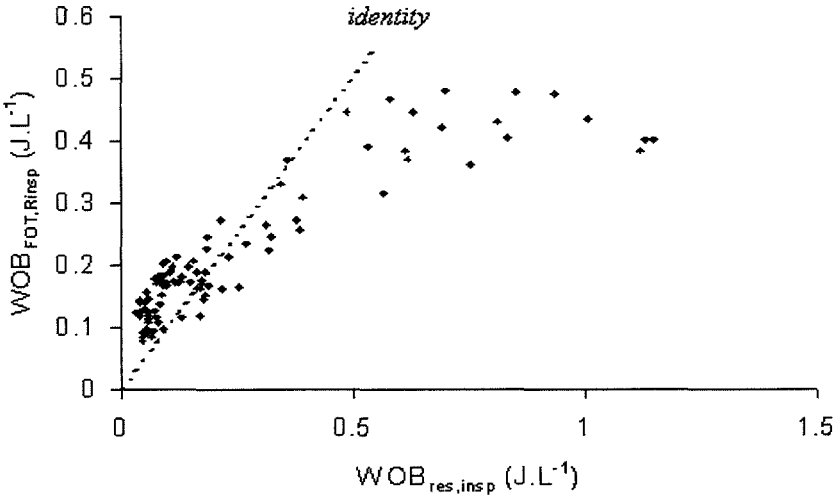


Table 2.1.2. Pearson correlation coefficients (r^2) relating oscillometry variables to those calculated from oesophageal manometry for the first five asthmatic subjects.

a) Resistance

	Oscillometry Parameters		
	R_{rs}	X_{rs}	Z_{rs}
$R_{L,insp}$	0.79	0.94	0.88
$R_{L,exp}$	0.59	0.92	0.83

b) Work of breathing

	Oscillometry Parameters		
	$WOB_{FOT,R}$	$WOB_{FOT,X}$	$WOB_{FOT,Z}$
$WOB_{res,insp}$	0.79	0.96	0.90
$WOB_{res,exp}$	0.56	0.92	0.83
WOB_{res}	0.77	0.96	0.90

Note:-

1. The appropriate inspiratory, expiratory or total component was used for correlating the oscillometry variables with the within-breath components of R_L and WOB_{res}.
2. All p-values < 0.0001

Figure 2.1.3. Data from the first five asthmatic subjects showing (a) $X_{rs,insp}$ plotted against $R_{L,insp}$ and (b) $WOB_{FOT,Xinsp}$ plotted against $WOB_{res,insp}$.
The lines of best fit to the data are shown with their equations and Pearson correlation coefficients.

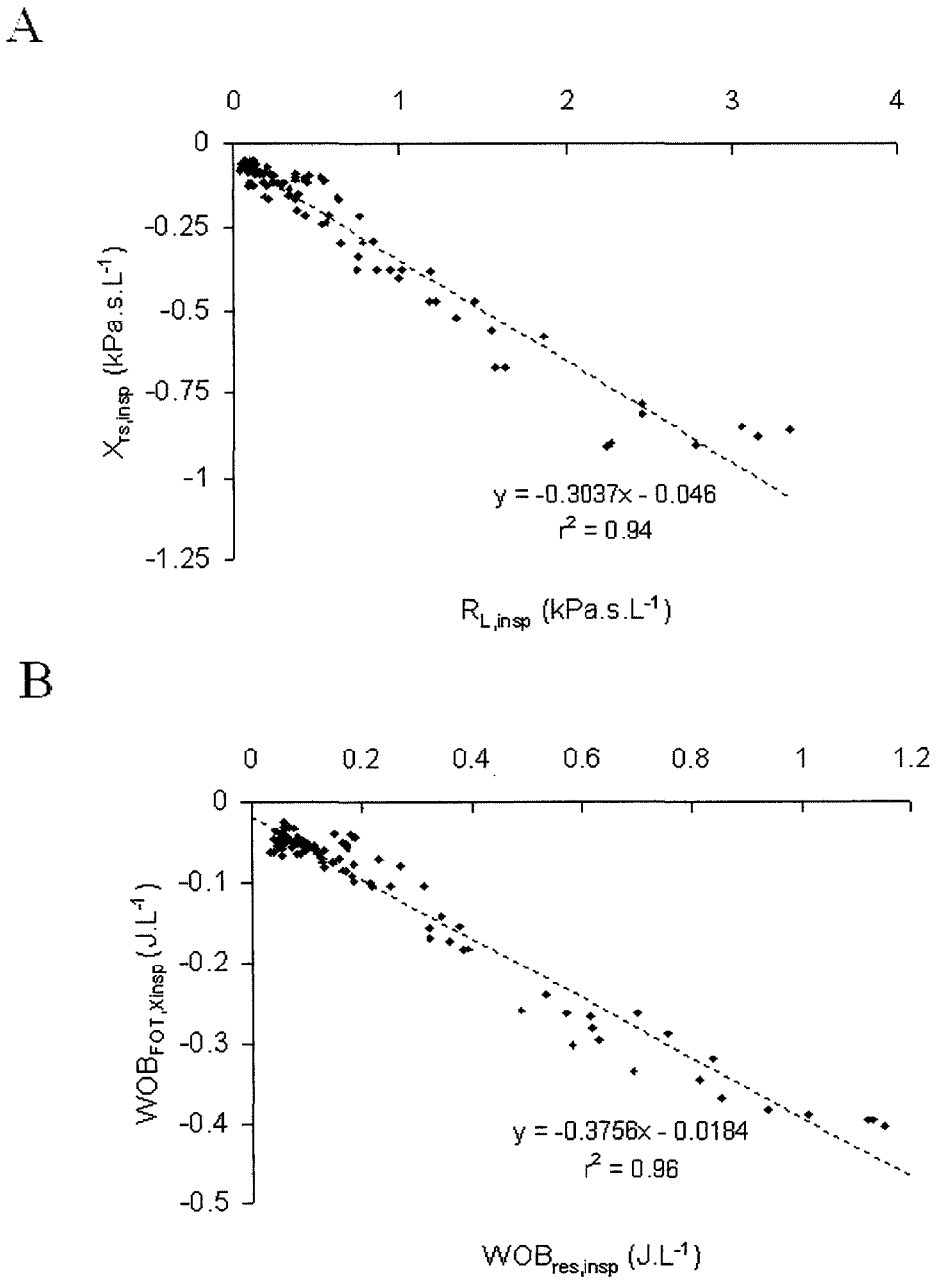


Figure 2.1.4. Data from the second set of six asthmatic subjects showing the accuracy of the prediction model derived from (a) $X_{rs,insp}$ for predicting $R_{L,insp}$ and (b) $WOB_{FOT,Xinsp}$ for predicting $WOB_{res,insp}$.

These are scatter plots of the difference between the predicted values of $R_{L,insp}$ and $WOB_{res,insp}$ (using the equations from Figure 2.1.3 derived from the first five asthmatics) and the actual values against the actual values. For comparison, the same plot using $R_{rs,insp}$ values is also shown. Mean (SD) difference values are shown for the values predicted from $X_{rs,insp}$ only.

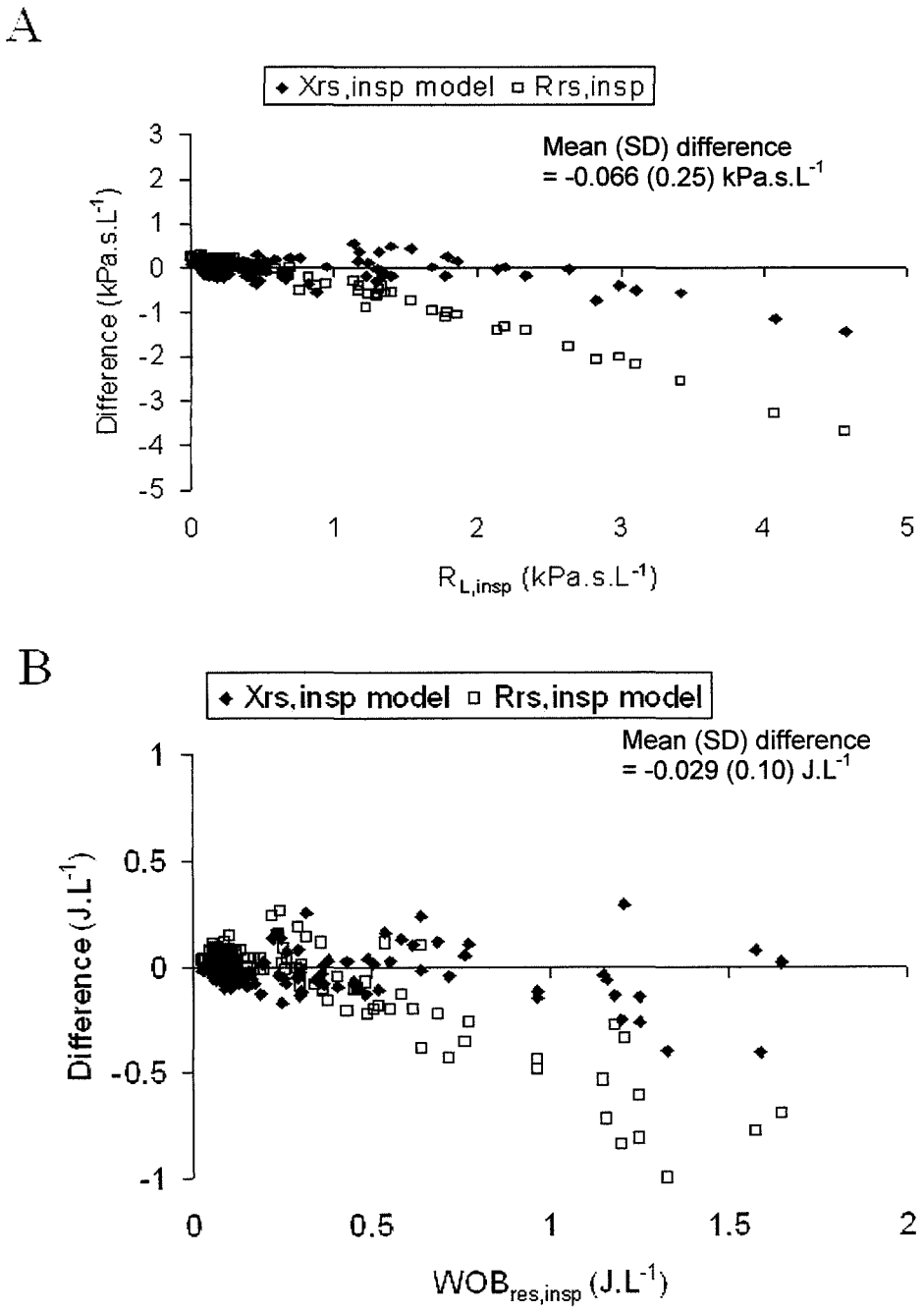
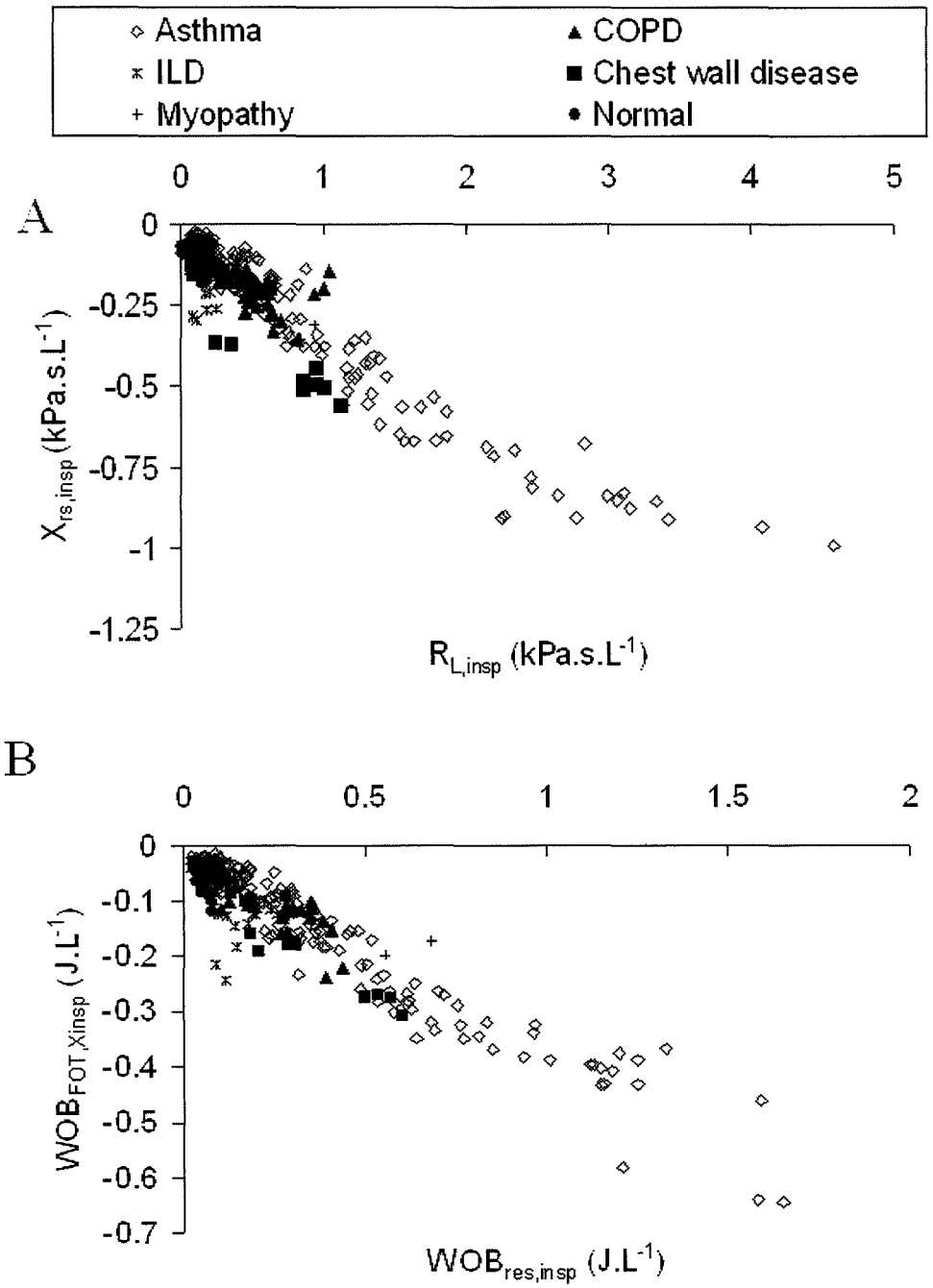


Figure 2.1.5. Data from all the subjects showing (a) $X_{rs,insp}$ plotted against $R_{L,insp}$ and (b) $WOB_{FOT,Xinsp}$ plotted against $WOB_{res,insp}$.



Repeatability

The repeatability values obtained for oesophageal manometry and oscillometry variables for the asthmatic and non-asthmatic subjects are shown in Table 2.1.3. The figures for the asthmatic subjects represent the worst case scenario as they are repeated measurements taken after each step of the histamine challenge test. In the period between doses of histamine, there is some variability of bronchoconstriction with time which will therefore inflate the quoted repeatability values. By contrast the non-asthmatic subjects were stable between measurements. These values for $R_{L,insp}$ and $R_{rs,insp}$ are similar to those quoted elsewhere for R_L and R_{rs}[4,217].

Table 2.1.3. Repeatability of key variables.

	Oesophageal Manometry		Oscillometry		
	$R_{L,insp}$	$WOB_{res,insp}$	$R_{rs,insp}$	$X_{rs,insp}$	$WOB_{FOT,Xinsp}$
Coefficient of Variation (%)					
- **Asthmatic subjects**	30	20	11	17	20
- **Non-asthmatic subjects**	22	15	8	12	13

Discussion

In this study an unconventional but carefully thought out approach has been taken to the use of oscillometry data. R_{rs} and X_{rs} were calculated as a function of time, separated into inspiratory and expiratory values for each breath and analysed in two ways. Firstly, the average inspiratory and expiratory values were compared with those from oesophageal manometry, $R_{L,insp}$ and $R_{L,exp}$. Secondly, the continuous values were combined with $\dot{V}^2$ and integrated over time to give a quantity with the units of work and again these were separated into inspiratory and expiratory values. Attention was focussed on the inspiratory integral as this reflects active resistive work. The use of expiratory values is complicated by the phenomenon of expiratory flow limitation which dissociates the relationship between pressure and flow. Despite this, when expiratory values were assessed, a similar pattern of results to inspiratory values were seen although the correlation coefficients dropped in magnitude

(Table 2.1.2). A single forcing frequency of 5 Hz was used as a compromise between limiting the errors attributable to breathing frequency and reducing the impact of upper airway wall shunt. Finally we analysed the usefulness of variables other than R_{rs} (i.e. X_{rs} and Z_{rs}) at estimating resistive properties.

Two interesting and perhaps surprising results have emerged from this study. Firstly the strongest predictor of $R_{L,insp}$ (and consequently $WOB_{res,insp}$) was not $R_{rs,insp}$ but a linear model using $X_{rs,insp}$. Secondly this relationship between $R_{L,insp}$ and $X_{rs,insp}$ appeared to be independent of the underlying disease process.

The first result is clearly supported by Figure 2.1.4. It would have been possible to use a fitted model for $R_{rs,insp}$ values instead of absolute values which would have improved its ability to predict $R_{L,insp}$ but this would not have performed as well as $X_{rs,insp}$. This fact is reflected in their relative correlation coefficients (Table 2.1.2) and can be seen from Figure 2.1.2. Here it is clear that the relationship between $R_{L,insp}$ and $R_{rs,insp}$ is curvilinear (and hence any fitted model would have to be nonlinear) and secondly the $R_{rs,insp}$ values would fan out from a fitted curve at higher values of $R_{L,insp}$ leading to poorer prediction of $R_{L,insp}$ at these values. For the asthmatic subjects, the "Bland-Altman" analysis for the $X_{rs,insp}$ values had a bias of -0.066 and standard deviation of ± 0.25 kPa.s.L^{-1}. The usefulness of this model can be assessed roughly by comparing the magnitude of the limits of agreement (± 0.5 kPa.s.L^{-1}) with the range of values seen (0-5 kPa.s.L^{-1}) which gives a ratio of ~10%. Similarly it was found that $WOB_{res,insp}$ was better predicted by a linear regression model using $WOB_{FOT,Xinsp}$ than by absolute values of $WOB_{FOT,Rinsp}$ which is also clearly shown in Figure 2.1.4 and a similar discussion to the above is appropriate. In this case the "Bland-Altman" analysis for the asthmatic subjects yielded a bias of -0.029 and a standard deviation of ± 0.1 J.L^{-1}. Compared with the range of values seen of 0-1.6 J.L^{-1}, this gives a ratio between the limits of agreement and the range of ~12.5%. One factor limiting the accuracy of $X_{rs,insp}$ as a predictor of $R_{L,insp}$ and $WOB_{res,insp}$ is its repeatability which is poorer than that of $R_{rs,insp}$ (Table 2.1.3). It is possible that this could be improved by attention to the technique of measurement, for example by increasing the amplitude of the forcing signal.

What is the mechanism underlying the strong linear relationship between $X_{rs,insp}$ and $R_{L,insp}$? It is not an isolated finding in this study as X_{rs} is known to become more negative with

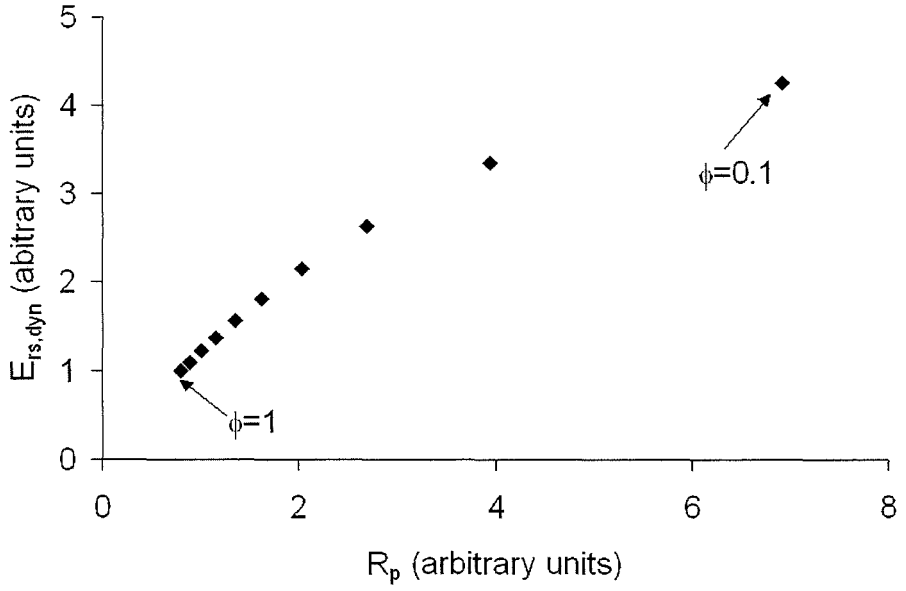
increasing airways obstruction. This has been shown in both the settings of COPD[226] and asthma[227] and lead to its proposal as an alternative measure during bronchial challenge testing[228]. The relationship between X_{rs} and R_{aw} or FEV_1 has been found to be stronger than for R_{rs}[219-221].

X_{rs} is composed of a contribution from both inertance and dynamic elastance ($E_{rs,dyn}$); $E_{rs,dyn}$ is the dominant term at a forcing frequency of 5 Hz. $E_{rs,dyn}$ is larger than static elastance ($E_{rs,st}$), the latter being measured under steady state conditions. The difference between $E_{rs,dyn}$ and $E_{rs,st}$ is accentuated by increasing flow rates or airway obstruction[39] and is attributable to several phenomena, viscoelasticity[12], time constant inhomogeneity (Otis effect)[14] and shunting by either the upper[118] or central[229] airway walls (Mead effect). The contribution from viscoelasticity occurs even in normal subjects and represents the time dependent resistive and elastic behaviour of the lung and chest wall tissues. Time constant inhomogeneity describes heterogeneity in mechanical properties in different areas of the lungs, usually as a consequence of underlying pathology, which leads to regional variations in rates of emptying of the lungs and the potential for air recirculation. Central and upper airway wall shunting occurs when the impedance of the lung periphery becomes comparable to the tissue impedance of the central and upper airway walls usually as a consequence of increasing distal airways obstruction or airway closure. Here upper airway refers to supraglottal and central to immediate subglottal structures.

Simulation studies have been performed to evaluate the relative influence of viscoelasticity, airway wall shunting and time constant inhomogeneity on $E_{rs,dyn}$. A sophisticated approach was taken by Lutchen et al.[171,230] who looked at $E_{rs,dyn}$ from breathing frequency to 5 Hz using a morphometric model of the lung. He predicted that increased bronchoconstriction could increase $E_{rs,dyn}$ in several ways. Firstly, homogeneous bronchoconstriction could produce a large increase in $E_{rs,dyn}$ by central airway wall shunting[230]. Secondly, severe inhomogeneous bronchoconstriction (with a greater than 80% reduction in calibre in a small number of airways) could produce a similarly large increase in $E_{rs,dyn}$ by the mechanism of time constant inhomogeneity[171]. The effect of viscoelasticity was detectable but more modest[230]. Support for the significance of heterogeneous bronchoconstriction is also present in a second model generated by Anafi et al.[231] which simulated the physical behaviour of a single peripheral airway taking into account airway flow and parenchyma and smooth muscle properties. This predicted that a constricted airway had two stable states, open and nearly closed, and lead

automatically to a two-compartment lung model and the situation of heterogeneous airways obstruction. The relationship between peripheral airway resistance and $E_{rs,dyn}$ predicted by this model when the proportion of closed airways was increased from zero to nearly complete is shown in Figure 2.1.6.

Figure 2.1.6. Relationship between peripheral airway resistance (R_p) and $E_{rs,dyn}$ using the two-compartment model proposed by Anafi et al.[231] when the proportion of open airways, ϕ, is decreased from 1 to 0.1 in steps of 0.1.



Less complex lumped element models representing time constant inhomogeneity and airway wall shunting have been used extensively in previous oscillometry studies to interpret R_{rs} and X_{rs} data usually presented as a function of frequency. The common conclusion of most of these studies[118,128,232-235] is that a model incorporating central airway wall compliance (Mead effect) fits the data better than one proposing parallel pathways (Otis effect) both qualitatively and as regards generating realistic physical values for the model coefficients. Further support for the significance of the Mead effect comes from data on expiratory flow limitation. This is the extreme case of the Mead model as the oscillometry forcing signal is unable to pass the flow-limited airway segments and instead is dissipated in the parallel impedances represented by the central and upper airway walls. In the recent study by Dellacà et al.[218], X_{rs} dropped dramatically in the presence of expiratory flow limitation (confirmed by oesophageal

pressure-flow loops). They were again able to simulate this effect using a lumped element model which allowed an airway wall shunt in parallel with airway and tissue compartments. The effect of expiratory flow limitation was reproduced when the resistance of the airways was increased from 0.05 to 25 kPa.s.L^{-1}.

Bronchoconstriction could also increase $E_{rs,dyn}$ by a direct effect on static tissue elastance due to changes in tissue properties[236] or airway closure but the magnitude of this component is uncertain and difficult to unravel from airway effects[230]. Studies attempting to partition airway and tissue properties conclude that the effect exists but is probably a lesser component of the increase in $E_{rs,dyn}$ seen during bronchoconstriction[235,237].

To determine the relative contributions of the different mechanisms to the decrease in X_{rs} with increasing R_L, the scenario was simulated here using a lumped element model at a single frequency of 5Hz which incorporated time constant inhomogeneity and both central and upper airway wall shunting. This model is described in detail in the Appendix 5. Representative values from the literature were chosen for the model parameter values and the only variable was the peripheral resistance, R_p, which was allowed to range over the values seen for R_L. The simulation results are shown compared with the experimental data from the first five asthmatic subjects in Figure 2.1.7. It can be seen that the model reproduces the qualitative behaviour of the data with the parameter values chosen and is also a reasonably accurate quantitative fit.

The simulation was then repeated incorporating one mechanism at a time and the results are shown in Figure 2.1.8(a). Heterogeneous parallel pathways on their own did not reproduce the X_{rs} behaviour, even when the time constants between the two pathways differed by several orders of magnitude. By contrast, introducing either upper or central airway wall shunt produced marked effects on X_{rs}, causing it to decrease as respiratory resistance increased. Initially both effects were of the same order of magnitude but at high levels of respiratory resistance the central airway wall shunt became relatively more important. The conclusion from these simulations was that both central and upper airway wall shunting were the major mechanisms dictating the linear relationship between X_{rs} and R_L at 5 Hz and time constant inhomogeneity had little effect. This conclusion should be viewed with a note of caution as, although it is in keeping with the previous lumped element modelling results[118,128,232-235], it is at variance with approaches using different forms of model[171,230,231]. It is possible that the

Otis effect does in fact have more impact on X_{rs} than shown in these simulations but that the lumped element model as implemented does not accurately reflect the in vivo phenomenon.

Why do all the subjects regardless of the nature of the respiratory pathology lie on the same curve? This result was not predicted beforehand as it was anticipated that lung diseases such as ILD and chest wall disease would have elevated $E_{rs,st}$ values and therefore the X_{rs} - R_L curve would shift significantly downwards. One suggestion to account for the observed behaviour is that the influence of R_L on X_{rs} is much larger than that due to $E_{rs,st}$ even when the latter is increased several fold. This explanation was supported by a further simulation (Figure 2.1.8(b)). Firstly lung elastance was decreased by a factor of five to simulate COPD (compliant lungs) which resulted in a small absolute increase in X_{rs}. Then elastance values were increased by a factor of five firstly for the lungs (stiff lungs) and then for the chest wall (stiff chest wall) to simulate ILD and chest wall disease respectively. The increased $E_{rs,st}$ values did shift the X_{rs} curve downwards but not greatly. The largest effect was at small resistance values where the change was of the order of -0.25 kPa.s.L^{-1} whilst at larger values a change of only –0.1 kPa.s.L^{-1} was seen. In retrospect this behaviour is also seen in the experimental data. Examining Figure 2.1.5, the X_{rs} values tended to be more negative than the group results in subjects with chest wall disease and ILD and less negative than the group in subjects with COPD.

Figure 2.1.7. The results of lumped element modelling compared with the experimental data from the first five asthmatic subjects for (a) $R_{rs,insp}$ and (b) $X_{rs,insp}$.
In the case of the simulation $R_{L,insp}$ is replaced by the respiratory resistance of the lumped element model, which was calculated from the sum of the central airway resistance (R_c), the chest wall resistance (R_w) and peripheral airway resistance (R_p). The values of R_c and R_w were constant and are given in Table A5.1. R_p is the real part of the sum of the impedances of the two peripheral pathways (Z_{p1} and Z_{p2}) (see Appendix 5 for further details).

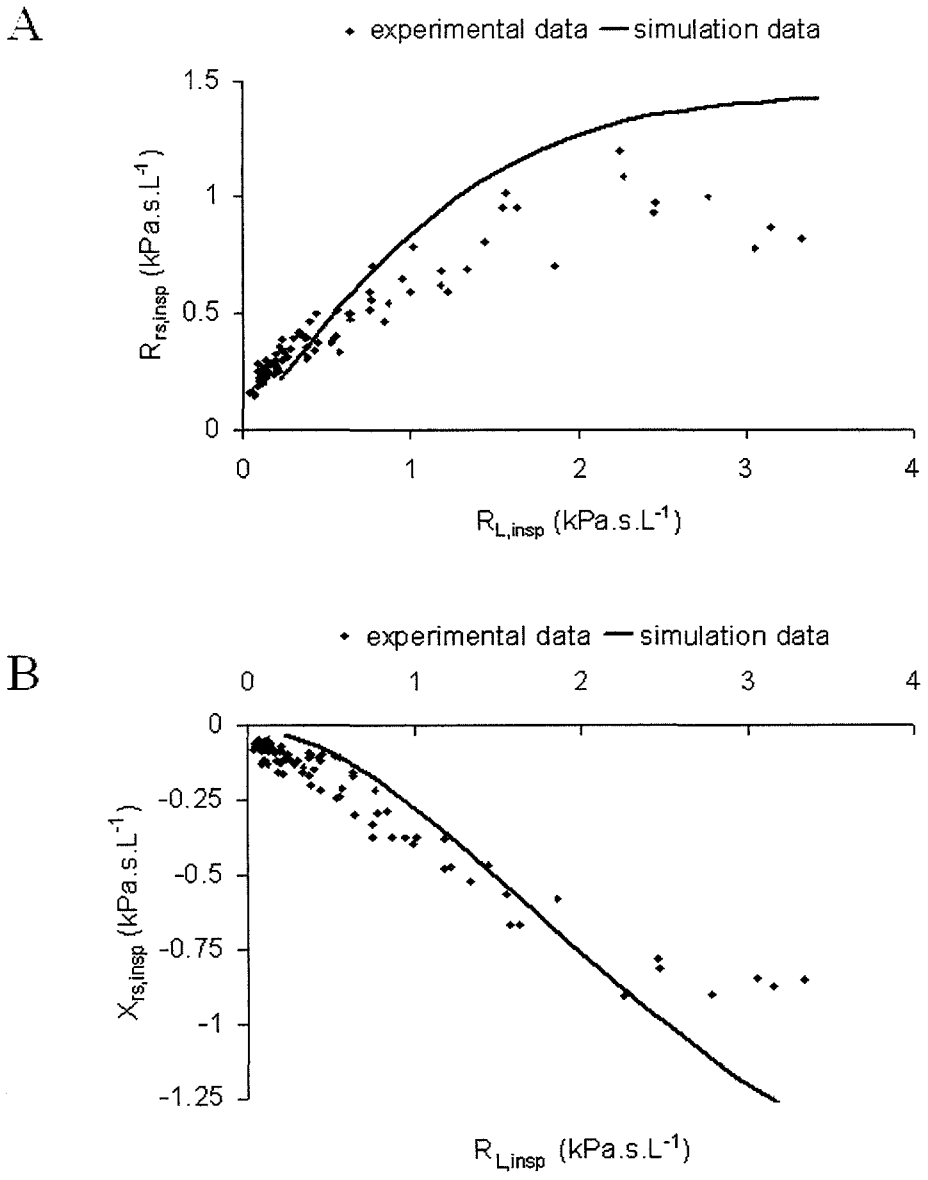
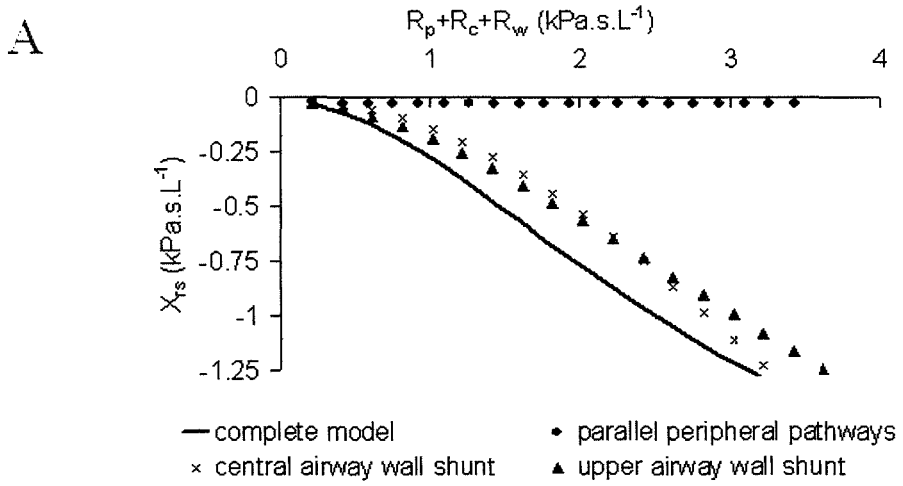
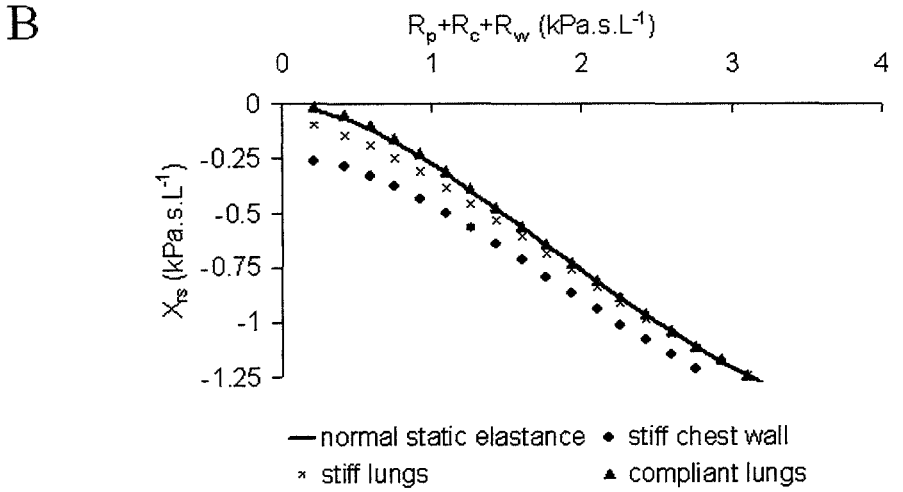


Figure 2.1.8 (a) Relative importance of three mechanisms (heterogeneous parallel pathways and upper and central airway wall shunting) contributing to the relationship between X_{rs} and respiratory resistance ($R_p+R_c+R_w$) illustrated by repeating the simulations with the three effects combined and in isolation. (b) Simulation of the effect on the relationship between X_{rs} and respiratory resistance ($R_p+R_c+R_w$) of changes in static elastance of the lungs or chest wall. Normal elastance is compared with a five-fold decrease in lung elastance (compliant lungs), a five-fold increase in lung elastance (stiff lungs) and a five-fold increase in chest wall elastance (stiff chest wall).





Conclusions

- The measured and simulated results in this study suggested that at 5 Hz the value of $X_{rs,insp}$ was linearly related to the airway resistance and, when used in an appropriate linear regression model, provided a more accurate estimate of $R_{L,insp}$ than absolute values of $R_{rs,insp}$.
- This behaviour extended to the prediction of $WOB_{res,insp}$ where a model based on the integral $WOB_{FOT,Xinsp}$ proved superior to absolute values of $WOB_{FOT,Rinsp}$. This could provide the basis for using forced oscillometry as a non-invasive estimate of work of breathing.
- The linear relationship between $R_{L,insp}$ and $X_{rs,insp}$ appeared to be independent of the disease process.
- Lumped element simulation suggested that this relationship between $R_{L,insp}$ and $X_{rs,insp}$ was due to central and upper airway wall shunting of the forcing signal which swamped any change in $X_{rs,insp}$ due to other physical properties such as elastance.

2.2 Evaluation of two non-invasive methods for measuring respiratory elastance in spontaneously breathing subjects

Introduction

Respiratory elastance (E_{rs}) comprises serial contributions from the lung parenchyma and the chest wall and is elevated in conditions which increase the stiffness of either of these components. This effect has been demonstrated in diseases affecting the lungs alone such as ILD[238,239], in conditions where there is a primary chest wall abnormality such as ankylosing spondylitis[158], kyphoscoliosis[240,241], thoracoplasty[159] or pleural thickening[242] and in situations where there is a restrictive defect without lung or chest wall disease such as obesity[80,156,158] or myopathy[154,243,244]. E_{rs} has clear potential as a measurement of severity and progression in such conditions[245,246]. Elastic work of breathing (WOB_{elas}) is closely related to E_{rs}, its value for each breath being estimated from the equation

$$W_{elas} = \frac{1}{2} E_{rs} V_T^{\,2}. \qquad \text{eqn 2.2.1}$$

It is therefore an alternative to E_{rs} incorporating additional information on breathing pattern.

E_{rs} and WOB_{elas} are not routinely measured in the pulmonary function laboratory because this process is invasive as described in Chapter 1.1. Two non-invasive methods for estimating these variables both based on positive pressure breathing were introduced in Chapter 1.2. The first[148] is an old method using a constant pressure over several breaths (CPAP) first described in 1956 by Heaf and Prime whereas the second[172] uses more complex mathematics (LSMLR) to look at small differences between adjacent pressure supported breaths (NIV). Such approaches to determining respiratory mechanics can nowadays be easily implemented with the combination of electronic non-invasive ventilators, digital signal recording and computerised analysis of results.

Aim

The aim of this study was to evaluate these two techniques for estimating E_{rs} (and thereby WOB_{elas}) in a modern setting by comparison with conventional measurements using appropriate method comparison methodology.

Methods

Study Design

E_{rs} was measured in two sets of subjects, the first set being from the pulmonary function laboratory and the second set intubated patients in ICU. The measurement was performed in three ways in each subject, by a conventional approach and by the two non-invasive methods (CPAP and NIV).

Subjects

To give values throughout the normal and pathological range, subjects with a variety of respiratory problems were recruited. In all, 66 subjects were studied, 20 ventilated patients in the intensive care unit (ICU) and 46 in the pulmonary function laboratory. The ventilated patients (age range 48 to 87 years) comprised 11 patients immediately following cardiothoracic surgery (7 coronary artery bypass grafting, 3 valve replacement and 1 excision of myxoma) and 9 requiring emergency ventilation for acute respiratory failure (3 acute respiratory distress syndrome, 3 respiratory failure post-surgery, 2 pneumonia and 1 cardiogenic pulmonary oedema). The laboratory subjects (Table 2.2.1) consisted of normals (7) and those with mild asthma (11), COPD (9), ILD (9), chest wall disease (8) and myopathy (2). This was the same group of subjects studied in the laboratory in Section 2.1.

Table 2.2.1. Subject characteristics.

	Number	Age (years)	FEV_1 (% pred)	FVC (% pred)	FEV_1/FVC (%)
Normal	7 (5 male)	27 (20-30)	97 (89-107)	98 (92 –108)	83 (79-88)
Asthma	11 (all male)	34 (28–47)	92 (69-112)	109 (82-123)	70 (62-82)
COPD	9 (8 male)	68 (53-73)	54 (31-107)	104 (70-160)	39 (25-52)
Myopathy[‡]	2 (no males)	62 (60-64)	63 (46-79)	68 (43-93)	81 (72-90)
ILD[§]	9 (4 male)	61 (50-75)	84 (50-122)	105 (50-130)	77 (59-80)
Chest wall disease[¶]	8 (3 male)	68 (49-78)	32 (27-40)	40 (31-66)	58 (39-92)

All values are median (range)

[‡]Mitochondrial myopathy (1), diaphragmatic palsy (1)

[§]Idiopathic pulmonary fibrosis (3), connective tissue disease (3), sarcoidosis (1), silicosis (1), hypersensitivity pneumonitis (1)

[¶]Kyphoscoliosis (4), thoracoplasty (3), pneumonectomy (1)

CPAP/NIV Methods

E_{rs} was measured non-invasively using both CPAP and NIV methods, performed twice on each subject. These techniques and their application in this study were described in detail in Chapter 1.2.

Conventional Methods in the ICU/Pulmonary Function Laboratory

In the ICU, conventional measurement of E_{rs} was performed with the subject on controlled ventilation. In the pulmonary function laboratory, E_{rs} was measured using a combination of oesophageal manometry to measure E_L and predicted values for E_{CW}. The theory and practical details of both these techniques were covered in Chapters 1.1 and 1.3.

Sample Size

No pilot data had been collected prior to the main study with which to perform this calculation. It was therefore presumed that similar numbers to that for the forced oscillometry study (Chapter 2.1) would be required in order to define adequately the performance of the methods.

Statistical Analysis

Statistical analyses were performed with StatView v 5.0.1 (SAS Institute Inc.). Correlation was calculated using Pearson's *r* correlation coefficients. The baseline characteristics of subjects have been given as median and range. Mean results were used to summarise the results on each patient group. Agreement of the results of the non-invasive with the conventional methods was assessed using an analysis similar to that proposed by Bland and Altman[225] and is indicated as "Bland-Altman". The repeatability of measurements was calculated as a coefficient of variation by expressing the standard deviation (SD) of the difference between repeated measurements as a percentage of the mean measurement.

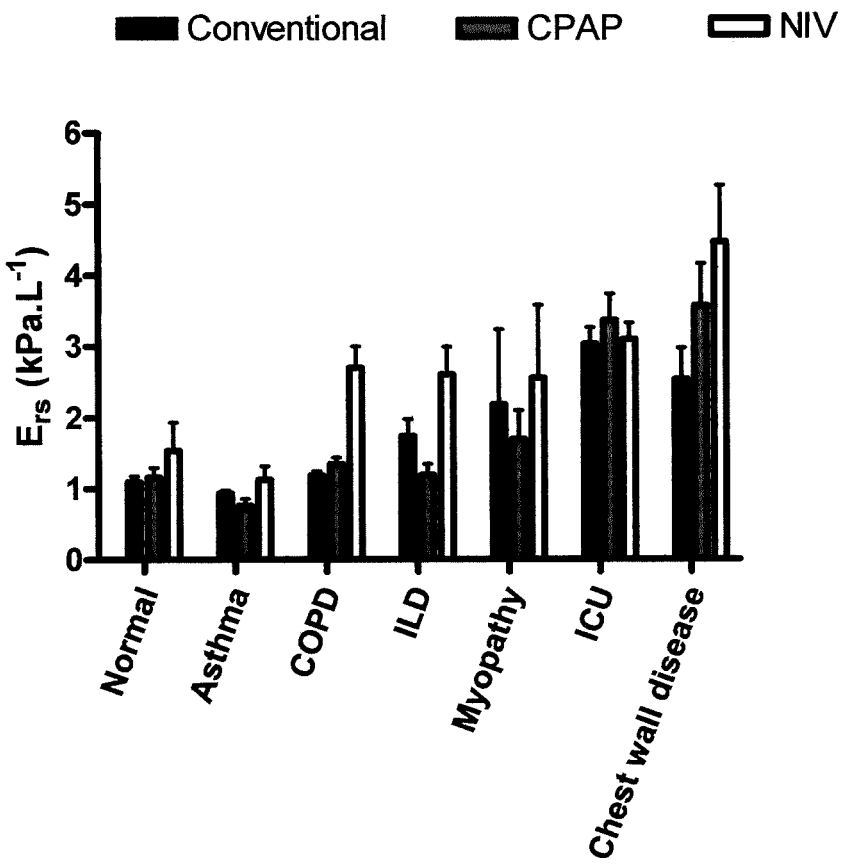
Results

The NIV method gave results for E_{rs} in all subjects whereas the CPAP method failed in 6 cases (9%) because no step in volume was detected when CPAP was applied. Five of these were ICU patients and one was a subject in the pulmonary function laboratory with ILD. On average, the CPAP method produced similar results to the control method whereas the NIV method consistently overestimated (Figure 2.2.1). The difference in results between the new and control methods for the chest wall disease patients is artificial. The control value in these subjects was generated by assuming a normal value for E_{CW} which is an underestimate.

The individual results for the NIV method are shown in Figure 2.2.2(a) (chest wall disease patients excluded). Correlation between NIV and control methods was significant (r=0.72,

p<0.0001). The outlying subject from ICU who suffered from morbid obesity artificially inflated this value and, if his result were excluded, the correlation coefficient fell (r=0.59, p<0.0001). The mean±SD difference between the two sets of results (Figure 2.2.1(b)) was 0.46±1.0 $kPa.L^{-1}$. Figure 2.2.3 performs the same analysis for the CPAP method. Correlation was higher (r=0.86, p<0.0001). The CPAP method had the better agreement particularly for lower values. The mean±SD difference between the CPAP and control methods was –0.007±0.69 $kPa.L^{-1}$. Individual results for the chest wall disease patients are shown in Figure 2.2.4. These were consistently above the line of identity suggesting that the non-invasive methods were successful at detecting elevated E_{CW}.

Figure 2.2.1. Mean E_{rs} values for each patient group using the non-invasive and control methods. Error bars show standard error of the mean (SEM).



The repeatability values obtained for elastance measured by oesophageal manometry and the non-invasive methods are shown in Table 2.2.2. These figures represent the worse case scenario as they reflect the repeatability of two measurements only. The process involved in a single measurement was defined in Chapter 1.2. In practice multiple measurements would be performed and averaged to give the final result for a subject.

Figure 2.2.2. (A) Individual E_{rs} results from the NIV method plotted against the conventional (conv) values. (B) Difference between E_{rs} value from the NIV method and the conventional value plotted against the conventional value.
(◆ Normal; ■ Asthma; ▲ COPD; × Myopathy; ✳ Interstitial lung disease; ● ICU; --- Identity)

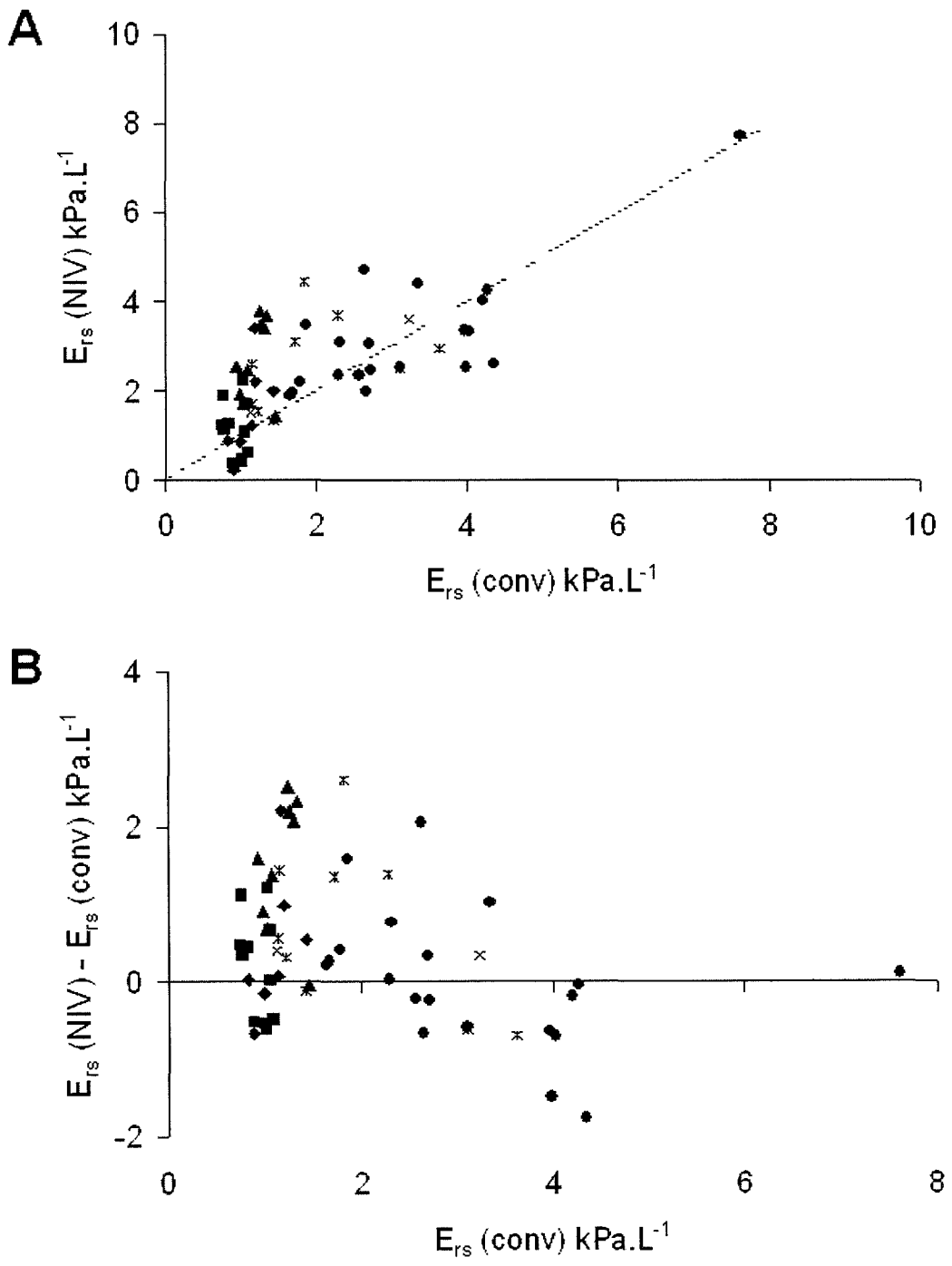


Figure 2.2.3. (A) Individual E_{rs} results from the CPAP method plotted against the conventional values. (B) Difference between E_{rs} value from the CPAP method and the conventional value plotted against the conventional value.
(◆ Normal; ■ Asthma; ▲ COPD; × Myopathy; ∗ Interstitial lung disease; ● ICU; --- Identity)

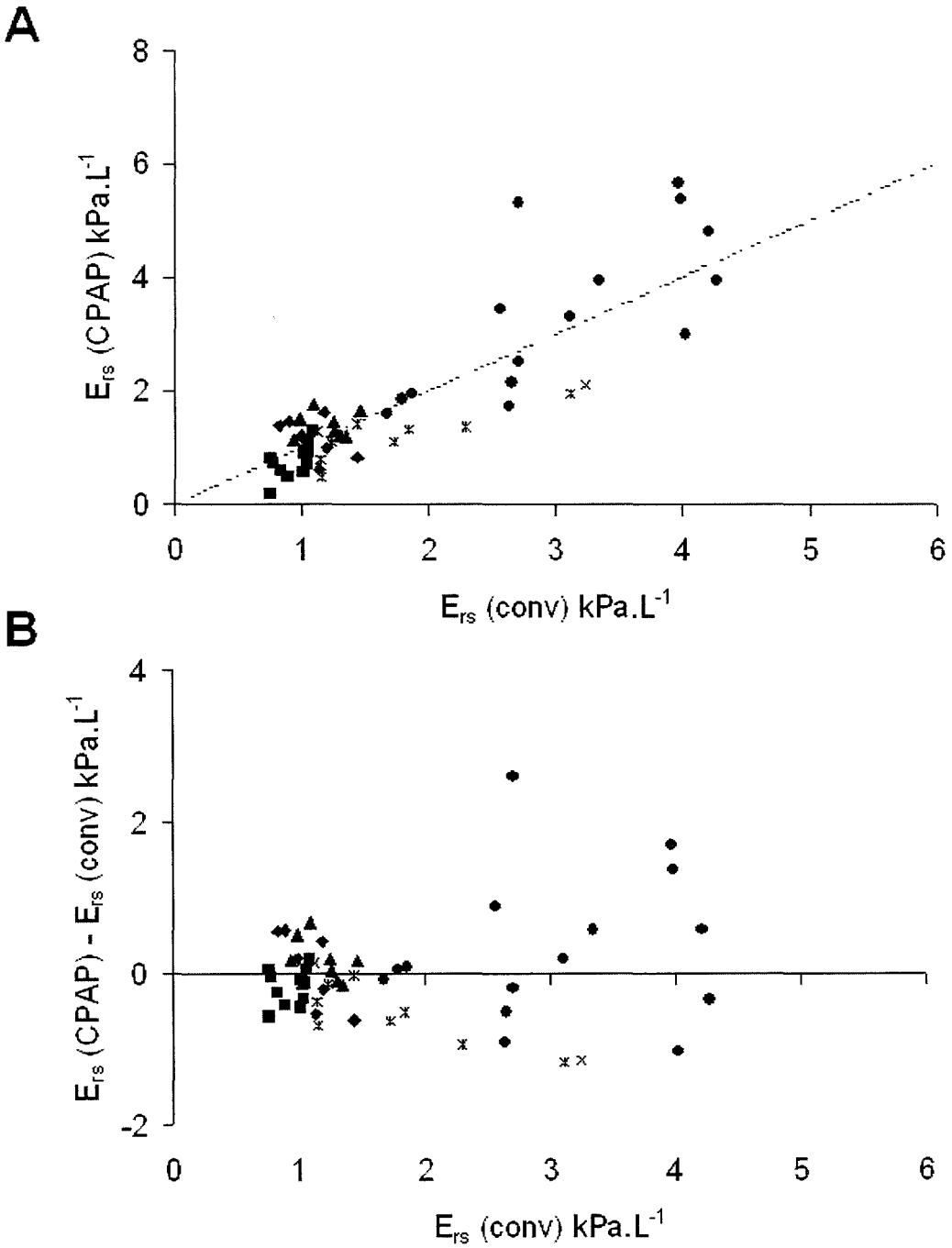


Figure 2.2.4. E_{rs} values for the patients with chest wall disease from the non-invasive and conventional methods.
Note that the conventional values are an underestimate because they assume normal chest wall elastance. (◆ CPAP; ■ NIV; --- Identity)

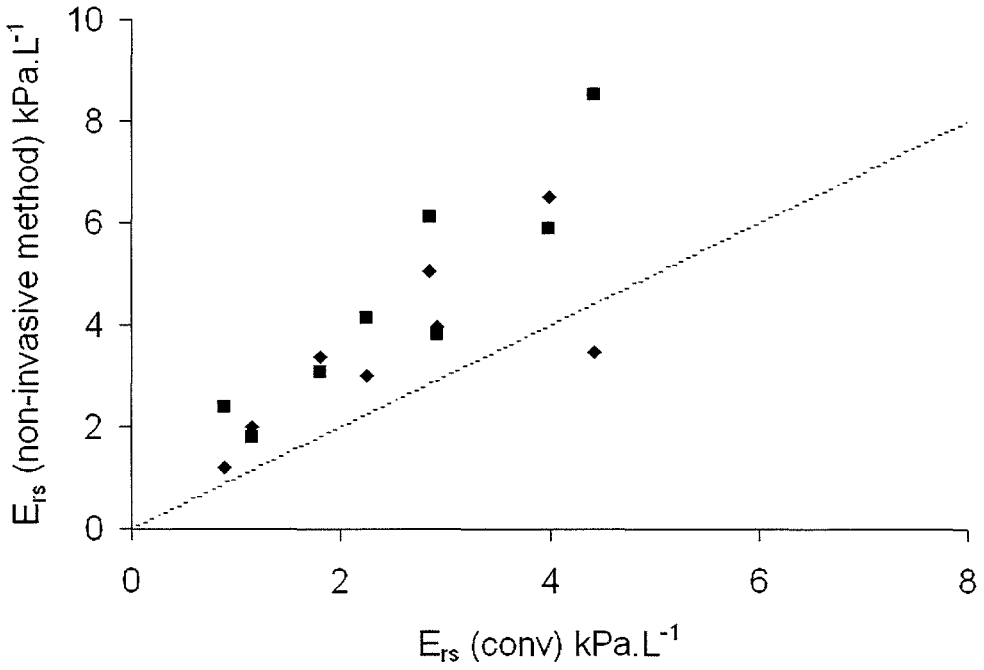


Table 2.2.2. Repeatability of E_{rs} values. The figure given for the conventional measurement is from oesophageal manometry.

	Method of Measurement		
	Conventional	**CPAP**	**NIV**
Coefficient of Variation (%)	8	24	36

Discussion

This study has evaluated two simple non-invasive techniques for measuring E_{rs} which use equipment widely available in all respiratory departments and procedures that require little cooperation, measuring only pressure and flow at the mouth during spontaneous tidal

breathing. The CPAP method was shown to be feasible in the 1950s-60s[148] but its relevance to modern practice has not been re-evaluated using the convenience of modern non-invasive ventilation equipment. By contrast the NIV method was proposed more recently. It has been evaluated by comparison with oesophageal manometry on patients in ICU[173] but in the pulmonary function laboratory it has only been validated using the forced oscillation technique as the control[172]. Each method took five to ten minutes to perform repeated measurements and was successfully carried out on the majority of patients, including those with severe COPD, ILD or chronic respiratory failure.

The "Bland-Altman" analysis for the CPAP method (Figure 2.2.3) showed a bias of –0.007 $kPa.L^{-1}$ and SD of 0.69 $kPa.L^{-1}$. The ratio of the limits of agreement (±1.4 $kPa.L^{-1}$) to the range (0-4.2 $kPa.L^{-1}$) was 33%. The data displayed better agreement at lower elastance values. For the NIV method, the "Bland-Altman" analysis gave a bias of 0.46 $kPa.L^{-1}$ and SD of 1.0 $kPa.L^{-1}$. The ratio of the limits of agreement (±2.0 $kPa.L^{-1}$) to the same range as for the CPAP method (0-4.2 $kPa.L^{-1}$) approached 50%. Repeatability showed the same pattern as accuracy, the CPAP method having a coefficient of variation of 24% and the NIV method 36%. In summary, the error involved with both techniques was large but despite this it was clear that the simpler CPAP method consistently outperformed the more complicated NIV method in terms of bias, limits of agreement and repeatability although it proved less reliable in the ICU population.

The scatter between the results from the non-invasive and control methods came from several sources:-

1. Although the time points of the conventional and non-invasive measurements were close to each other, they were not performed simultaneously and hence there was potential for the measurement conditions (i.e. ventilatory flow, thoracic volume and respiratory rate) to have changed between the application of the methods. Dynamic elastance is known to be dependent on such parameters and its value would be affected by the conditions prevailing at the time of measurement.
2. All three methods relied on simplifying assumptions to give a single value of E_{rs}. The conventional and CPAP methods assumed a constant E_{rs} value over the tidal volume. The NIV method assumed a simple linear one-compartment two-component model for the respiratory system which has limited validity in the context of significant respiratory

pathology, although the analysis of small perturbations to linearise the problem should have reduced this error.

3. Air leaks during the application of positive pressure were a further source of error. A constant leak would not have affected the algorithm used to calculate E_{rs} but a variable leak would have introduced an error.
4. Variations in respiratory muscle effort caused an increase in scatter. The NIV method assumed the same muscular effort for the first 0.5 s of breaths that were compared. In practice there was always involuntary variation which was compounded by voluntary differences when the subject reacted to the difference in inspiratory pressure. To minimise this problem the subjects were asked to put the same effort into every breath. The CPAP method required an absence or similar degree of expiratory effort at end-expiration both with and without the CPAP. To achieve this the subjects were asked to breathe uniformly with the same effort regardless of the pressures applied at the mouthpiece. The validity of these assumptions was not directly assessed during the study but inferred from the agreement between the conventional and non-invasive methods.
5. A factor affecting the success of the CPAP method in the ICU patients was the presence of intrinsic PEEP. If this were much greater than the external PEEP, then addition of further PEEP in the form of a CPAP pulse would have had an unpredictable effect on thoracic volume, in some cases not increasing it, and this might account for the clustering of failures of the CPAP method in the ICU group.
6. Sedation differed between the methods in the ICU subjects.
7. No attention was paid to the elastic behaviour of the upper airway (i.e. cheeks and pharynx) which are partially under voluntary control and could affect results.

These sources of error were exaggerated at high levels of E_{rs} where the signal to noise ratio is relatively poor. Changes in airway pressure with both these methods were largely independent of the value of E_{rs}. By contrast, changes in thoracic volume were inversely proportional to E_{rs} and hence smaller at high values. This made both methods less accurate with high E_{rs} values, where the volume change threatened to disappear in the biological noise.

Modifications could be made to improve the accuracy of these methods. In particular, altering the way in which positive pressure is applied could reduce variations in muscular effort. For example, with the NIV method, a high value of inspiratory pressure would reduce or even abolish muscular effort and then every 30 seconds the inspiratory pressure could be lowered for one breath rather than being increased. In addition, there were a number of

choices taken in defining the algorithm for the NIV method which could potentially be improved upon with further investigation. Examples include the location of the point of alignment of low and high pressure breaths and the duration of the period of comparison (an empirical interval of 0.5 s was used here). There is scope also to optimise signal to noise ratios by tailoring the size of the change in inspiratory pressure or of the pulse in CPAP to the anticipated elastance value. Other avenues include minimising air leaks, performing more measurements to obtain a more accurate average value and more prolonged training of the subjects.

Conclusions

- The results of this study suggest that both of these non-invasive tests for measuring E_{rs} have potential for routine use in the pulmonary function laboratory.
- The NIV method could distinguish between subjects with normal and abnormal E_{rs} values but accuracy was not sufficient to separate gradations of abnormality.
- The CPAP method clearly showed superior performance and was the more promising candidate for further development.

Part 3: Evaluation of non-invasive techniques for measuring work of breathing

3.1 Assessment of bronchodilator reversibility

Introduction

Bronchodilator reversibility is usually assessed in patients with airways obstruction by looking at changes in FEV_1 and FVC post-bronchodilator, the aim being either to distinguish between patients with asthma and COPD or to predict the benefit to be expected from bronchodilator therapy. There is a strong body of evidence which disputes the ability of the acute bronchodilator response assessed by change in FEV_1 to predict the long-term therapeutic benefit of bronchodilation in COPD. In the absence of a significant change in FEV_1 post bronchodilator, it is possible to detect acute changes in other resting pulmonary function tests (such as expiratory flow-volume loops[247], IC[3,248] inspiratory muscle activity[249] or pressure-time products[250]), in functional capacity assessed by exercise performance[3,251-255] and in dyspnoea scales[3,250,253,254,256-259]. It is also possible to find evidence of long-term therapeutic benefit from bronchodilation measured by PEF, spirometry, exercise tolerance, symptoms and quality of life[256,260-263].

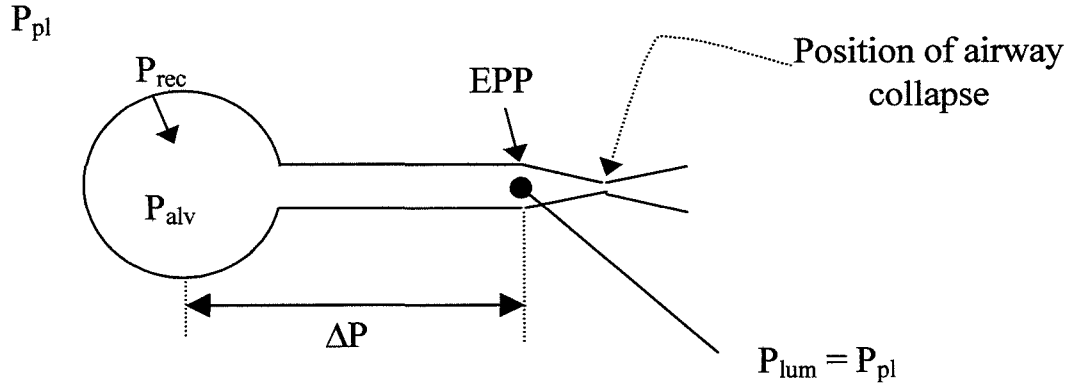
One reason why FEV_1 is not more successful in this context is that it is not a simple surrogate measure of resistance but has more complex physiology[264]. During a forced expiratory effort in a normal person, only the first fifth of the expiratory volume is effort dependent as the procedure is flow-limited for the remainder of expiration with the maximum flow rate defined by the lung volume[265]. This can be understood by considering pressure in the alveolus as the sum of pleural pressure and pressure due to lung elastic recoil (Figure 3.1.1). Moving along the airways towards the mouth, pressure progressively drops from alveolar pressure to atmospheric for two reasons.

- Firstly, the area of the airways diminishes and, to conserve mass, the flow of air must increase[266]. To cause the air to accelerate (termed convective acceleration), a pressure gradient is required. This effect is dominant at larger volumes.
- Secondly, the airways offer resistance to air flow and a pressure gradient is required to overcome frictional losses[267]. This effect is relatively more important at low volumes.

Airway collapse occurs when the pleural pressure exceeds the luminal pressure in the intrathoracic airway by an amount sufficient to overcome the supporting tension provided by

the lung parenchyma. Flow is therefore limited to the maximum that does not cause airway collapse and any further increase in effort would not increase flow. The point at which airway collapse occurs is just downstream of the equal pressure point (EPP) described by Mead[268] (where luminal airway pressure equals pleural pressure) and its location (and the associated maximum flow) will vary with lung elastic recoil pressure, the upstream resistance and the mechanical properties of the airway wall. In COPD, there is increased compliance due to loss of elastic tissue, increased resistance due to airway narrowing and loss of parenchymal support for airways allowing them to collapse more easily[269]. Expiratory flow limitation therefore occurs earlier in the forced expiration, which reduces peak expiratory flow, and, at any lung volume, the upstream airway characteristics of COPD cause a lower flow than that seen in normal lungs. This leads to the pathognomic appearance of the expiratory limb of the flow volume loop[270].

Figure 3.1.1. Schematic illustration of the concept of flow-limitation due to flow-dependent airway collapse.
P_{pl}, P_{alv} and P_{rec} are pleural, alveolar and lung elastic recoil pressure respectively. EPP is the equal pressure point and P_{lum} is the airway pressure at that point.



$$P_{alv} = P_{rec} + P_{pl}$$

$$\Delta P = P_{rec}$$

It is now recognised that bronchodilators achieve benefit not only by reducing resistance but also by decreasing hyperinflation and the possibility of using measurements of hyperinflation to assess bronchodilator response has been studied over the last two to three

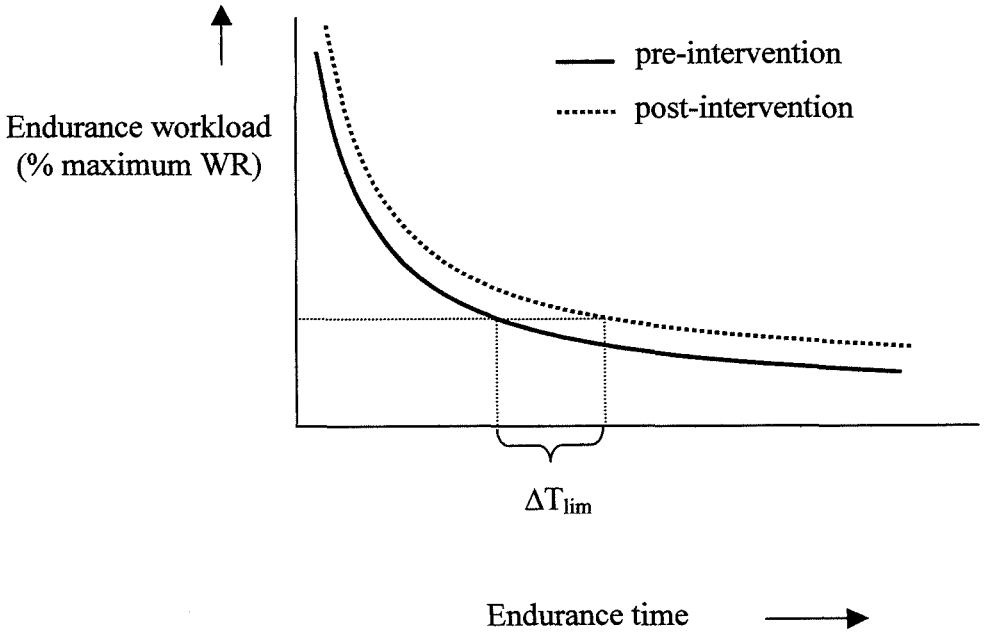
decades[3,248,255,271-278]. One such variable is IC, which diminishes with increasing severity of COPD either due to rising functional residual capacity (FRC) or an elevated EELV caused by dynamic hyperinflation. One study looked at the ability of bronchodilator induced changes in lung volumes to predict change in exercise capacity measured by constant workload cycle ergometer tests and found that change in IC or inspiratory reserve volume (IRV) were significant predictors whereas change in FVC, FEV_1 and peak expiratory flow rate were not[3]. Change in IC has proved responsive to all existing forms of inhaled bronchodilators[3,274,277,279,280] in both acute and chronic test scenarios. Some studies, however, suggest that it may only be of use when tidal breathing is flow-limited as it is only in this context that bronchodilators would increase tidal flow and allow patients to breathe at lower lung volumes[247,281-283].

Exercise capacity is another attractive outcome measure as it quantifies function rather than resting physiology and potentially has greater relevance to the patient. As a tool for assessing acute bronchodilator effect, it has recently been subjected to systematic review[284] but the study outcomes appeared rather heterogeneous. There was a significant increase in exercise capacity in 11 out of 18 studies of anticholinergic agents, 7 out of 14 studies of short-acting β_2 agonists, 1 study of formoterol, none of 3 studies of salmeterol and 1 of 8 studies of theophylline. This inconsistency has continued in several modern studies performed since the publication of the systematic review[250,279,280,285]. One explanation for this inconsistency is that exercise capacity in COPD is dependent not only on lung volumes which dictate ventilatory capacity[286-289] but also on ventilation/perfusion mismatching (i.e. wasted ventilation)[290], skeletal muscle dysfunction[286,289,291] or deconditioning (i.e. increased ventilatory demand for the same workload)[286,292,293], cardiac function and volition[294]. A more intriguing possibility raised in a very recent study was that the ability to convert a bronchodilator effect into improved exercise capacity in COPD depended on the way in which the chest wall muscles adapted to the changes produced by the bronchodilator[285]. Subjects who permitted dynamic hyperinflation were more likely to experience benefit from the bronchodilator.

It may be possible to improve the consistency of benefit seen with bronchodilators in exercise testing by using a different exercise test design such as the constant workload endurance test which may more closely reflect the impact of an intervention on activities of daily living. Most of the studies in the systematic review used either an incremental exercise test or a fixed

time walking tests. The former is designed to elicit maximum exercise capacity. The latter evokes a physiological response which lies somewhere between a constant workload endurance test and an incremental test[295-298]. More recently it has been demonstrated that the constant workload endurance test is much more sensitive to both physical (exercise training) and pharmacological (bronchodilator) interventions[3,279,280,295,299,300]. For example, in a three way comparison of incremental cycle ergometer test, six minute walk test and cycle endurance test, oxitropium produced a 19% increase in endurance time, a 1% increase in six minute walk distance and no increase in VO_{2peak}[295]. Such tests may also have more relevance to subjects as they are more likely to reflect the submaximal effort involved in activities of daily living. The greater sensitivity of endurance tests is due to the hyperbolic relationship between workload and exercise time (see Figure 3.1.2). Using this approach, O'Donnell has systematically demonstrated positive bronchodilator effects due to ipratropium, tiotropium and salmeterol on endurance exercise times[3,279,280].

Figure 3.1.2. Relationship between workload and exercise time (T_{lim}) in an endurance exercise test.
A small change in this relationship resulting from an intervention can have an amplified effect on ΔT_{lim}.



Dynamic hyperinflation during exercise (due to expiratory flow limited tidal breathing) is thought to be one of the principal mechanisms limiting ventilatory and therefore exercise capacity in COPD[258,301,302] and it can be measured by serial IC values during the exercise test[258]. This phenomenon has two consequences. Firstly, a reduction in IC limits maximum ventilation as V_T cannot exceed IC and any further increase in minute ventilation can only be achieved by greater respiratory frequency. Secondly, the phenomenon of neuromechanical dissociation occurs. As the lungs work at higher and higher EELV, the inspiratory muscles become less efficient, the respiratory system less compliant and intrinsic PEEP constitutes a progressively greater inspiratory workload. Despite increased respiratory muscle effort compared with a normal person, total ventilation is significantly lower. Bronchodilators can relieve this problem and increase maximum minute ventilation by enabling the subject to maintain the same ventilation at lower operational lung volumes.

Dyspnoea is a further outcome measure of greater importance to subjects than their lung volume values. In one-stop acute testing of bronchodilator effect the most useful vehicle is a visual analogue scale such as the Borg score[199] with dyspnoea produced by a stimulus such as exercise. Serial Borg scores have been taken during endurance exercise testing and changes in isotime Borg score post-bronchodilator can be detected even if there is no change in resting FEV_1[258].

In Chapter 2.1 it was shown that $X_{rs,insp}$ at 5Hz was strongly correlated with $R_{L,insp}$, much more so than $R_{rs,insp}$. A similar relationship held between $WOB_{res,insp}$ and $WOB_{FOT,Xinsp}$. Both these oscillometry parameters would be expected to be directly responsive to bronchodilator effect. In addition $X_{rs,exp}$ has recently been shown to be a sensitive and specific marker of expiratory flow limitation during tidal breathing in COPD with the suggestion that it could be used to quantify the proportion of expiratory time over which flow-limitation occurs[218]. Again this quantity would be expected to diminish post-bronchodilator and be directly related to dynamic hyperinflation at rest. Early studies demonstrated that bronchodilator use in single COPD patients could be seen as changes in oscillometry parameters[118,303]. Since then a number of studies have reproduced this effect in larger groups of patients[216,226,304-308]. The studies are consistent in that they show a larger effect of bronchodilation on X_{rs} based parameters compared with R_{rs}. The consistency of these oscillometry studies ends there. Some used frequency ranges over which to average oscillometry parameters[226,307,308] whereas others used values at single frequencies[216,305,306]. Some including the largest study did not

look at X_{rs} values[216,305,308] and none performed within-breath analysis. Their conclusions regarding the usefulness of FOT at assessing bronchodilator response in COPD relative to spirometry and plethysmography are also heterogeneous[216,308].

Aim

The aim of this study was to explore the ability of within breath oscillometry measurements to provide information on acute therapeutic benefit of bronchodilators when compared with spirometry and with more recently evaluated tests which have a potentially greater link to subjective outcomes of importance to patients (such as hyperinflation, exercise tolerance and dyspnoea).

Methods

Subjects

Target recruitment was 40 subjects to complete the protocol. Forty-four were enrolled. Three dropped out after the initial visit and one after the second visit (due to recurrence of an inguinal hernia) and these patients were not included in the results. The inclusion criteria were the presence of airways obstruction on routine spirometry (i.e. pre-bronchodilator FEV_1/VC ratio less than 1.96 residual standard deviations below the predicted value[309]) and age $\geq$ 18 years. This allowed the recruitment of subjects with airway obstruction for any cause. Exclusion criteria were any medical conditions or physical disability which precluded or limited the ability to perform a cycle exercise test. The study population was recruited from patients attending for routine pulmonary function tests at GRI between February 2002 and February 2003.

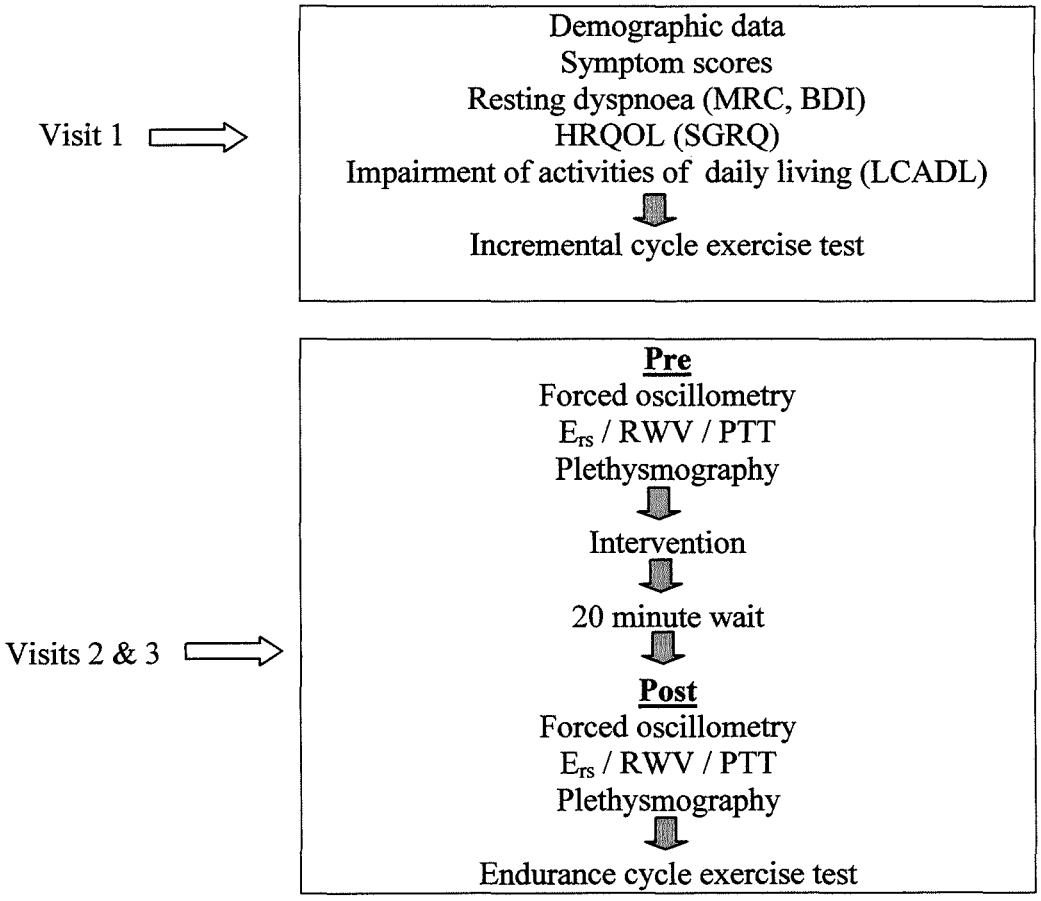
Study Design

The methodology was very similar to that described by O'Donnell et al. in a number of recent studies in this area[3,279,280]. The study had a randomised, placebo-controlled, crossover design and the protocol is summarised in Figure 3.1.3. There were three visits with a minimum of two days between each visit. The aim of visit 1 was to familiarise the subject with cycle exercise tests and to determine maximum work rate by an incremental cycle exercise test. The aim of visits 2 and 3 was to determine the effect of bronchodilator (5 mg salbutamol) compared with placebo (0.9% sterile sodium chloride solution) on resting pulmonary function tests and endurance (constant workload) cycle exercise tests. To achieve this, the pulmonary function tests were performed pre and 20 minutes post an intervention which was randomly assigned as bronchodilator on one visit and placebo on the other. The intervention drug was delivered over 10 to 15 minutes in a 2.5 ml volume using a jet nebulizer (Micro-Neb Nebuliser, Lifecare Hospital Supplies) driven by an airflow of 8 $L.min^{-1}$ (Aquilon Nebuliser System, AFP Medical) through a face mask (Duo Mask Adult, Lifecare Hospital Supplies). Randomisation was by alternate allocation of subjects to placebo or active bronchodilator as the first intervention in order of enrolment. The pulmonary function tests were (in order of execution) forced oscillometry, E_{rs}, RWV, PTT and body plethysmography. All the tests described in Chapter 1.2 were performed and analysed (including E_{rs} and WOB_{elas}). Only oscillometry, RWV and PTT results are shown as these are the relevant variables in an obstructive setting. Dellaca's study[218] had suggested several indices for quantifying % flow limitation (%FL) from $X_{rs,exp}$. In this study %FL was calculated from the proportion of the expiratory time for which $X_{rs,exp} < -0.7$ $kPa.s.L^{-1}$. In practice this meant that the percentage of each expiratory breath that was flow limited was determined and this percentage was averaged over all the breaths contained in the oscillometry recording. Not surprisingly E_{rs} and WOB_{elas} showed no change post-bronchodilator. The exercise test was performed after the pulmonary function tests and post-intervention only. After a period of rest and then unloaded cycling, the subject cycled at a workload of 80% of that achieved during their earlier incremental cycle exercise test. During the test, serial measurements of IC to assess dynamic hyperinflation and Borg score to assess dyspnoea and leg fatigue were taken each minute. All conventional physiological tests are described in detail in Chapter 1.3.

Study tests were double blinded except for the operator supervising forced oscillometry, E_{rs}, RWV and PTT which were single blinded to the subject. Analysis of all results was double

blinded. Subjects were asked to avoid major physical exertion and to omit inhaled bronchodilators on the day of investigation (tiotropium was not available at that time) and omit oral bronchodilators for 24 hours. Compliance with this request was ascertained verbally on the day of the visit. For each subject the tests were performed at the same time of day.

Figure 3.1.3. Study protocol.



Sample Size

Since little was known beforehand regarding the likely magnitude and scatter of changes in X_{rs} and work of breathing, the study was powered to detect a small (10%) change in R_{rs}. The change in R_{rs} expected was ~0.05 kPa.s.L^{-1} with a standard deviation for the change of ~0.15 kPa.s.L^{-1}, assuming a coefficient of variation of the measurement of ~10-15%. Therefore, to

detect this change with 80% power and a significance level of 0.05, the sample size required was 35[310,311].

Statistical Analysis

Results were summarised either as mean (SD) or median (IQR). Variables were screened for normality using the Shapiro-Wilk W Test. Comparisons were performed using the Student's paired t test except where the variable was not normal or not continuous when the Wilcoxon signed rank sum test was used[310]. The level of statistical significance was taken as 0.05. No compensation for multiple comparisons (such as the Bonferroni method) has been explicitly applied and this should be taken into consideration when interpreting the significance of results. The effect of the crossover design on the results of the study was assessed by checking for period effects and treatment-period interactions[310]. Between day reproducibility of the test results was assessed by looking at the difference in pre-bronchodilator results. These were analysed in two ways

- as coefficient of variation, i.e. the standard deviation of the difference between repeated measurements divided by the mean measurement expressed as a percentage[312]
- by an intraclass correlation coefficient of reliability[313]. $R<0.4$ indicates poor reliability, $0.4 \leq R \leq 0.75$ fair to good reliability and $R>0.75$ excellent reliability.

Spearman's rank correlation coefficients were calculated to identify whether any of the changes in the resting pulmonary function tests were associated with increased T_{lim}, $V_{E,end}$ or reduced $Borg_{dysp,iso}$. All statistics where performed with Statview v 5.0.1 (SAS Institute Inc.) with the exception of intraclass correlation where SPSS v 12.0.1 (SPSS Inc., Chicago, Illinois, USA) was used.

Results

Baseline Characteristics

The baseline characteristics of the study population are shown in Table 3.1.1. The aim of the entry criteria was to select a representative population of patients with airways obstruction attending for pulmonary function tests at GRI who would conventionally go on to have

reversibility studies (similar to Sourk[314]). Thirty-six of our subjects had a clinical history and baseline pulmonary function tests consistent with a diagnosis of COPD[315]. A further two had asthma and two allergic bronchopulmonary aspergillosis. The clinical diagnosis was supported by the study PFT results which showed that only the two asthmatics attained normal FEV_1/VC ratios with all other subjects showing a degree of irreversible airflow obstruction. In addition the minimum smoking history of the current or ex-smokers was 10 pack years and the minimum age was 52. This selection of COPD patients almost certainly reflected the entry criteria (the presence of significant airflow obstruction on screening), the location of the study (the East end of Glasgow with its high prevalence of COPD) and the requirement of three study visits which was not favoured by younger, employed, asthmatic patients.

The study population had a median FEV_1 of 50.7% predicted, suggesting that approximately half the subjects had moderate to severe airflow obstruction using the BTS/NICE grading definition[315]. The incremental exercise test results showed a reduced peak work rate with ventilatory rather than cardiovascular (low BR and high HRR) limitation to be expected in this group. The subjects were also significantly symptomatic from the airways disease with measurable exacerbation rate, symptoms (symptom score), limiting dyspnoea (MRC, BDI), impairment of ability to perform activities of daily living (LCADL) and reduction in health related quality of life (SGRQ). There were equal numbers receiving either placebo or bronchodilator as the first intervention.

Period Effects and Treatment-period Interactions

No significant treatment-period interactions were revealed. Three variables were found to have a significant period effect, namely isotime Borg score for breathlessness ($p=0.036$), isotime Borg score for leg fatigue ($p=0.025$) and $R_{rs,exp}$($p=0.04$). The difference in Borg scores arose because of lower values on average at visit 2 compared with visit 3 (average $Borg_{dysp,iso}$ of 5.5 v 6.2 respectively) and could reflect a learning effect. There was no obvious explanation for the significant result for $R_{rs,exp}$. This detectable period effect was not deemed to require a change in the analysis method of the study results as it was small in magnitude, affected a few results only and had impact on both treatment and placebo arms.

Table 3.1.1. Baseline characteristics of study patients.

	Mean (SD)
Sex (male : female)	29 : 11
Age (years)	64.6 (7.1)
Clinical diagnosis (COPD : ABPA : asthma)	36 : 2 : 2
Weight (kg)	74.8 (17.8)
Height (m)	1.67 (0.10)
BMI ($kg.m^{-2}$)	26.3 (4.7)
Smoking history	
- **ex or current smokers : lifelong non-smokers**	38 : 2
- **pack years**	49 (27)
Spirometry	
- **VC (L)**	3.35 (0.87)
- **FEV_1 (L)**	1.45 (0.54)
- **FEV_1 (% pred)**	54 (17)
- **FEV_1/VC (%)**	42 (10)
Incremental cycle exercise test: peak exercise values	
WR (W)	76 (44)
VO_2 ($L.min^{-1}$)	1.07 (0.47)
(% pred)	65.2 (33.5)
HR (min^{-1})	125 (17)
HRR (min^{-1})	30.4 (17.5)
RR (min^{-1})	33.3 (5.4)
V_E ($L.min^{-1}$)	45.8 (18.3)
(% MVV)	82.9 (20.8)
BR (% MVV)	17.1 (20.8)
R	1.15 (0.14)
Exacerbation frequency (yr^{-1})	2 (1-5)$^{\infty}$
Symptom score	6.03 (2.73)
Dyspnoea	
- **BDI**	5.13 (3.28)
- **MRC**	2.83 (1.01)
Impairment of activities of daily living (LCADL)	31.6 (11.4)
HRQOL (SGRQ)	
- **Symptoms**	73.3 (23.8)
- **Activities**	68.9 (25.0)
- **Impacts**	44.1 (23.4)
- **Total**	56.5 (22.0)

$^{\infty}$Median (IQR)

Reproducibility

The availability of baseline results pre intervention for the two visits gave the opportunity to define the comparative between visit reproducibility or reliability of the resting pulmonary function tests (Table 3.1.2). The coefficients of variation for the lung volume variables (FEV_1, VC, IC) were similar to those quoted elsewhere[255]. The values for the R_{rs} derived variables were similar to the figure of 15% for R_{rs6} measured by van Noord[216]. In the latter study they did achieve better values for R_{aw}, sG_{aw}, FEV_1 and FVC but this could perhaps be explained by a difference in study population, ours being more severely obstructed. The intraclass correlation coefficient of reliability, R, was also calculated. If this exceeded 0.75, it was deemed to indicate excellent reliability or reproducibility[313]. All of the plethysmographic, oscillometry and pulse transit time measurements satisfied this criterion other than $WOB_{FOT,Xinsp}$ which had a value of 0.744. The order of reliability was plethysmography > oscillometry > pulse transit time. E_{rs} and RWV were not reliable in this patient group.

Table 3.1.2. Reproducibility analysis. Pre-bronchodilator data from visits 2 and 3.

	Mean pre-bronchodilator value		Coefficient of Variation	Intraclass R
	Visit 2	Visit 3	(%)	
Plethysmography				
VC (L)	3.336	3.333	7.2	0.945
FEV_1 (L)	1.419	1.431	9.6	0.955
FEV_1/VC (%)	42.13	42.33	6.8	0.940
RV (L)	3.572	3.542	9.8	0.863
TLC (L)	6.906	6.876	4.5	0.955
IC (L)	2.257	2.211	8.8	0.912
R_{aw} ($kPa.s.L^{-1}$)	0.4666	0.4688	23.0	0.771
sG_{aw} ($kPa^{-1}.s^{-1}$)	0.5540	0.5275	22.6	0.850
Oscillometry				
R_{rs} ($kPa.s.L^{-1}$)	0.5393	0.5334	12.2	0.822
X_{rs} ($kPa.s.L^{-1}$)	-0.3919	-0.3843	24.1	0.852
$R_{rs,insp}$ ($kPa.s.L^{-1}$)	0.4760	0.4671	14.0	0.849
$X_{rs,insp}$ ($kPa.s.L^{-1}$)	-0.2085	-0.2104	17.6	0.850
$R_{rs,exp}$ ($kPa.s.L^{-1}$)	0.5838	0.5799	13.2	0.778
$X_{rs,exp}$ ($kPa.s.L^{-1}$)	-0.5136	-0.4989	28.6	0.841
$WOB_{FOT,Xinsp}$ ($J.L^{-1}$)	0.5283	0.5240	27.1	0.744
%FL (%)	30.51	28.14	53.9	0.830
Pulse transit time				
ΔPTT_{max} (ms)	8.811	8.584	44.3	0.802
ΔPTT_{ave} (ms)	4.821	4.995	60.4	0.791
Respiratory waveform variation				
RWV_{diff} (AU)	56.14	54.67	41.5	0.720
RWV_{area} (AU)	28.52	27.72	44.5	0.764

Treatment Effect

Changes in variables have been given both as absolute values and percentage change, where the latter was calculated from the absolute change divided by the mean of the two values. The exceptions to this were the lung volumes where the change was expressed as a percentage of predicted values to avoid bias associated with those patients with lower baseline values.

Treatment effect on resting tests was calculated in two ways, firstly from the between-day difference postbronchodilator and placebo and secondly from the within-day difference pre and post bronchodilator. The former gives a true indication of therapeutic effect controlling for the impact of maximal manoeuvres on airway calibre whilst the latter represents the typical clinical setting of bronchodilator reversibility testing. Only the between day results are shown (Table 3.1.3). All plethysmographic and oscillometry parameters showed significant changes between placebo and bronchodilator except for TLC. Absolute change in PTT was also significant. The within-day results were largely similar to the between-day changes except that change in TLC was also significant and the changes in oscillometry R_{rs} values were smaller with $R_{rs,exp}$ being non-significant. There were no treatment effects in RWV in either analysis and these measurements were not analysed further.

For the exercise data, only the between-day difference is available and the results are shown in Table 3.1.4. These showed significant increases with bronchodilator in T_{lim}, $V_{E,end}$ and IC during unloaded exercise ($IC_{unloaded}$). Analysis of the isotime variables showed significant increase in V_T, V_E, IC, IRV, V_E/VO_2 and V_E/VCO_2. The end-exercise variables showed the same behaviour with the addition of increases in VO_2 and HR. There was a drop in isotime Borg score which was significant only as a % change.

The largest % change following treatment was seen in resistive parameters and T_{lim} in the endurance test in the following order (from Table 3.1.3: $X_{rs,exp} > sG_{aw} > X_{rs} > R_{aw} > X_{rs,insp} > R_{rs,insp} > WOB_{FOT,Xinsp} > T_{lim} > R_{rs} > R_{rs,exp}$). By comparison changes in plethysmographic volumes were smaller and in the order RV > IC > FEV_1 > VC > FEV_1/VC > TLC. This pattern of change is similar to that seen in other reversibility studies[3,216,248,275,295,306] although the placement of within-breath X_{rs} values within the order is new.

Table 3.1.3. Effect of bronchodilator on resting tests: between-day analysis of salbutamol vs placebo.

		Absolute Change		% Change	
		Mean	p-value	Mean	p-value
Plethysmography					
VC	**(L)**	**0.216***	**<0.0001**	**6.8+***	**<0.0001**
FEV_1	**(L**	**0.224**	**<0.0001**	**8.7+**	**<0.0001**
FEV_1/VC	**(%)**	**3.600**	**<0.0001**	**4.8+**	**<0.0001**
RV	**(L)**	**-0.272**	**0.001**	**-12.4+**	**0.0009**
TLC	**(L)**	-0.055	NS	-0.869+	NS
IC	**(L)**	**0.277***	**<0.0001**	**10.7+**	**<0.0001**
R_{aw}	**($kPa.s.L^{-1}$)**	**-0.143**	**<0.0001**	**-33.1**	**<0.0001**
sG_{aw}	**($kPa^{-1}.s^{-1}$)**	**0.252***	**<0.0001**	**37.7**	**<0.0001**
Oscillometry					
R_{rs}	**($kPa.s.L^{-1}$)**	**-0.107**	**<0.0001**	**-20.4***	**<0.0001**
X_{rs}	**($kPa.s.L^{-1}$)**	**0.120**	**<0.0001**	**37.1**	**<0.0001**
$R_{rs,insp}$	**($kPa.s.L^{-1}$)**	**-0.116**	**<0.0001**	**-25.4**	**<0.0001**
$X_{rs,insp}$	**($kPa.s.L^{-1}$)**	**0.057***	**<0.0001**	**29.0**	**<0.0001**
$R_{rs,exp}$	**($kPa.s.L^{-1}$)**	**-0.101**	**<0.0001**	**-18.0***	**<0.0001**
$X_{rs,exp}$	**($kPa.s.L^{-1}$)**	**0.161**	**<0.0001**	**40.1**	**<0.0001**
$WOB_{FOT,Xinsp}$	**($J.L^{-1}$)**	**-0.056***	**0.0005**	**-22.0***	**0.002**
% FL	**(%)**	**-15.4***	**<0.0001**		
Pulse transit time					
ΔPTT_{max}	**(ms)**	**-2**	**0.005**	**33.6***	**0.03**
ΔPTT_{ave}	**(ms)**	**-2***	**0.006**	**-74.8***	**0.03**
Respiratory waveform variation					
RWV_{diff}	**(AU)**	-1	NS	0.2	NS
RWV_{area}	**(AU)**	-1	NS	-0.5	NS

+ % predicted

* Non-parametric test used (Wilcoxon signed rank for absolute changes, one sample sign test for % changes)

Table 3.1.4. Effect of bronchodilator on endurance exercise tests: salbutamol vs placebo - changes

	Placebo	Salbutamol			
		Absolute Change		% Change	
	Mean (SD)	Mean	p-value	Mean	p-value
T_{lim} (s)	303 (198)	73*	0.0004	20.5	0.001
$IC_{unloaded}$ (L)	2.26 (0.73)	0.21	<0.0001	9.3	<0.0001
Isotime variables					
VO_2 (ml.min^{-1})	1070 (450)	21*	NS	2.2	NS
VCO_2 (ml.min^{-1})	1150 (530)	10*	NS	1.2	NS
HR (min^{-1})	117 (22)	1	NS	1.0	NS
RR (min^{-1})	32.3 (6.1)	-1*	NS	-2.3	NS
V_T (L)	1.34 (0.56)	0.12	<0.0001	9.4	<0.0001
V_E (L.min^{-1})	42.0 (17.6)	2.4*	0.002	6.0	0.003
IC (L)	1.87 (0.70)	0.16	0.02	7.4	NS
$Borg_{dysp}$	6.13 (2.38)	-0.6*	NS (0.06)	-13.1*	0.03
$Borg_{leg}$	6.73 (2.63)	-0.7*	NS (0.06)	-13.0*	0.05
IRV (L)	0.529 (0.256)	0.09*	0.002	13.9*	0.001
ΔEELV (L)	-0.387 (0.317)	0.01	NS	43.4*	NS
V_E/VO_2	39.5 (6.2)	1.5	0.005	3.8	0.006
V_E/VCO_2	37.9 (6.2)	1.9	0.0001	4.8	0.0001
End-exercise variables					
VO_2 (ml.min^{-1})	1090 (450)	40	0.045	4.0	0.02
VCO_2 (ml.min^{-1})	1160 (520)	20	NS	2.7	NS
HR (min^{-1})	122 (20)	3.7	0.02	3.1	0.01
RR (min^{-1})	33.9 (6.3)	1*	NS	2.5*	NS
V_T (L)	1.33 (0.56)	0.09	0.0005	6.9	0.0008
V_E (L.min^{-1})	43.7 (17.8)	3.3*	0.006	8.1	0.0001
IC (L)	1.83 (0.70)	0.19	<0.0001	10.7*	<0.0001
$Borg_{dysp}$	7.93 (1.85)	0.03*	NS	-1.6*	NS
$Borg_{leg}$	8.08 (2.16)	0.15*	NS	2.7*	NS
IRV (L)	0.504 (0.278)	0.10*	0.006	10.9*	0.006
ΔEELV (L)	-0.428 (0.293)	-0.02	NS	30.9*	NS
V_E/VO_2	40.5 (7.25)	1.7	0.003	4.1	0.008
V_E/VCO_2	38.7 (6.72)	2.2	0.0001	5.4	0.0005

*Non-parametric test used (Wilcoxon signed rank for absolute changes, one sample sign test for % changes)

Predicting Therapeutic Benefit

The potential for acute bronchodilator reversibility tests to predict therapeutic benefit for patients was assessed by looking at the association between changes in resting pulmonary function tests and exercise parameters (Table 3.1.5). The exercise parameters chosen for comparison were T_{lim} as a measure of exercise capacity, $Borg_{dysp,iso}$ to give an indication of breathlessness during exercise and $V_{E,end}$ as a measure of ventilatory capacity. ΔT_{lim} and $\Delta Borg_{dysp,iso}$ had the same distribution of associations with exercise parameters but no association with resting pulmonary function test changes. By contrast $\Delta V_{E,end}$ was associated with flow related exercise parameters and also showed significant associations with both ΔIC and changes in resistive parameters (R_{aw}, $1/sG_{aw}$, $X_{rs,insp}$) especially when represented as % change. Multiple linear regression analysis showed that the linear combination of IC with a resistive parameter did not lead to a strengthened association. It was notable that ΔFEV_1 was not associated with $\Delta V_{E,end.}$

Table 3.1.5. Correlation coefficients: exercise test and resting pulmonary function tests. Spearman's rank correlation coefficients are given (r_S). Coefficients for VC, FEV1/VC, RV and TLC were all non-significant and are not included.

		ΔT_{lim}		$\Delta V_{E,end}$		$\Delta Borg_{dysp,iso}$	
		sec	%	L.min^{-1}	%		%
Plethysmography							
ΔFEV_1	(L)	NS	NS	NS	NS	NS	NS
ΔIC	(L)	NS	NS	**0.392**	**0.367**	NS	NS
ΔR_{aw}	(kPa.s.L^{-1})	NS	NS	**-0.417**	**-0.489**	NS	NS
$\Delta(1/sG_{aw})$	(kPa.s)	NS	NS	**-0.380**	**-0.451**	NS	NS
Oscillometry							
ΔR_{rs}	(kPa.s.L^{-1})	NS	NS	NS	NS	NS	NS
ΔX_{rs}	(kPa.s.L^{-1})	NS	NS	NS	NS	NS	NS
$\Delta R_{rs,insp}$	(kPa.s.L^{-1})	NS	NS	NS	**-0.315**	NS	NS
$\Delta X_{rs,insp}$	(kPa.s.L^{-1})	NS	NS	**0.389**	**0.359**	NS	NS
$\Delta R_{rs,exp}$	(kPa.s.L^{-1})	NS	NS	NS	NS	NS	NS
$\Delta X_{rs,exp}$	(kPa.s.L^{-1})	NS	NS	NS	NS	NS	NS
$\Delta WOB_{FOT,Xinsp}$	(J.L^{-1})	NS	NS	NS	NS	NS	NS
Pulse transit time							
ΔPTT_{max}	(ms)	NS	NS	NS	NS	NS	NS
ΔPTT_{ave}	(ms)	NS	NS	NS	NS	NS	NS
Endurance exercise test - Isotime variables							
ΔVO_2	(ml.min^{-1})	NS		**0.483**		NS	
ΔVCO_2	(ml.min^{-1})	**-0.332**		**0.531**		NS	
ΔHR	(min^{-1})	NS		NS		NS	
ΔRR	(min^{-1})	**-0.367**		NS		**0.485**	
ΔV_T	(L)	NS		**0.356**		NS	
ΔV_E	(L.min^{-1})	**-0.432**		**0.645**		**0.495**	
ΔIC	(L)	NS		NS		NS	
$\Delta Borg_{dysp}$		**-0.483**		NS		-	
$\Delta Borg_{leg}$		**-0.522**		NS		**0.609**	
$\Delta V_E/VO_2$		**-0.427**		NS		**0.451**	
$\Delta V_E/VCO_2$		**-0.325**		NS		**0.362**	

Predicting Bronchodilator Response

For each pulmonary function variable, the definition of bronchodilator response could be created in two principle ways

- from reproducibility data[216,312]
- from placebo responses[314,316].

The latter has the advantage that it takes into account any effect that the physical performance of the test has on the post-test measurement and was the approach taken here.

The size of the placebo effect was determined by the within-day difference pre and post 0.9% sodium chloride solution. There were small but significant changes in FEV_1/VC, RV and sG_{aw} but sizeable increases in all R_{rs} parameters and a decrease in $X_{rs,insp}$, suggesting measurable bronchoconstriction induced by placebo testing. A level defining a significant response to bronchodilator was derived for each test measurement (Table 3.1.6) based on the 95% confidence intervals generated from the placebo results for a sample size of 40 (i.e. 2.02 x SD)[314]. The number of responders generated by each test are shown in Table 3.1.7. FEV_1 and sG_{aw} were the most sensitive single parameters. Since the subjects identified as having a bronchodilator response were not the same for each test, combining terms (e.g. absolute or % changes, ΔIC or ΔsG_{aw}) lead to greater sensitivity as shown.

Table 3.1.6. Minimum values for a positive bronchodilator response defined from the 95% confidence intervals for the placebo response.

		95% CIs for placebo response	
		Absolute change	% change
Plethysmography			
VC	**(ml)**	+365	+10*
FEV_1	**(ml)**	+235	+8*
FEV_1/VC	**(%)**	+3.9	+5*
RV	**(ml)**	-652	-29*
TLC	**(ml)**	-594	-10*
IC	**(ml)**	+400	+15*
R_{aw}	**($kPa.s.L^{-1}$)**	-0.195	-34
sG_{aw}	**($kPa^{-1}.s^{-1}$)**	+0.229	+35
Oscillometry			
R_{rs}	**($kPa.s.L^{-1}$)**	-0.101	-16
X_{rs}	**($kPa.s.L^{-1}$)**	+0.150	+39
$R_{rs,insp}$	**($kPa.s.L^{-1}$)**	-0.088	-19
$X_{rs,insp}$	**($kPa.s.L^{-1}$)**	+0.069	+31
$R_{rs,exp}$	**($kPa.s.L^{-1}$)**	-0.122	-17
$X_{rs,exp}$	**($kPa.s.L^{-1}$)**	+0.217	+44
$WOB_{FOT,Xinsp}$	**($J.L^{-1}$)**	-0.345	-71
%FL	**(%)**	-27	
Pulse transit time			
ΔPTT_{max}	**(ms)**	-9.07	
ΔPTT_{ave}	**(ms)**	-6.59	

* % predicted

Table 3.1.7. Number of responders (using response defined by upper limit of placebo effect).

	Absolute change	% change	Combined (OR)
VC	8	12	13
FEV_1	17	17	18
FEV_1/VC	14		
RV	9	8	9
TLC	4	5	5
IC	6	7	9
R_{aw}	5	14	14
sG_{aw}	17	16	18
R_{rs}	7	8	9
X_{rs}	9	11	15
$R_{rs,insp}$	11	11	13
$X_{rs,insp}$	6	14	16
$R_{rs,exp}$	4	7	8
$X_{rs,exp}$	8	10	14
$WOB_{FOT,Xinsp}$	2	4	5
% FL	6		
ΔPTT_{max}	0		
ΔPTT_{ave}	0		
IC *or* FEV_1			23
IC *or* sG_{aw}			22
IC *or* $X_{rs,insp}$			20
IC *or* $X_{rs,insp}$ *or* $X_{rs,exp}$			25
FEV_1 *or* sG_{aw}			23
FEV_1 *or* $X_{rs,insp}$ *or* $X_{rs,exp}$			25
IC *or* FEV_1 *or* sG_{aw}			27
IC *or* FEV_1 *or* $X_{rs,insp}$ *or* $X_{rs,exp}$			27

Discussion

This study confirms that the effect of bronchodilator in COPD subjects can be demonstrated as a group mean change in plethysmography and forced oscillometry variables, the latter being larger percentage changes counterbalanced by worse reproducibility.

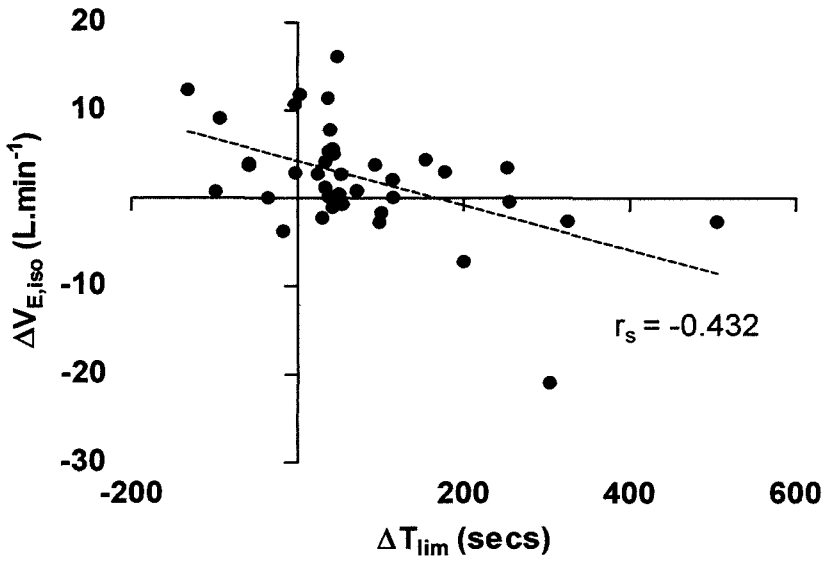
The pattern of change in endurance exercise testing reported in the literature has evolved as experience with this test modality has increased. Initially an increase in T_{lim} with no change in $V_{E,end}$ and a reduction in RR_{iso} was reported[3]. However, more recent studies have shown changes identical in pattern and very similar in magnitude to our data, namely a 19-58% increase in T_{lim}, a 5-10% increase in $V_{E,end}$ and a pattern at isotime of increased V_T, no change in RR and decreased Borg scores[279,280,295]. In this study bronchodilator generated an increase in exercise capacity (T_{lim}: 20.5%) and ventilatory capacity ($V_{E,end}$: 8.1%). The increase in $V_{E,end}$ was achieved by an increase in $V_{T,end}$ (6.9%) in the context of an increased IC_{end} (10.7%) consistent with an improvement in respiratory mechanics due to reduced hyperinflation. End-exercise cardiovascular stress was increased (shown by the increase in HR) whereas there was no change in respiratory rate. At isotime, bronchodilator reduced breathlessness ($Borg_{dysp,iso}$: -13.1%). However, $V_{E,iso}$ was increased (6.0%) with no change in $VO_{2,iso}$, leading to an increase in ventilatory equivalents. This suggested that bronchodilator worsened ventilatory efficiency, which most commonly is due to either greater ventilation–perfusion mismatch or hyperventilation.

From the correlation analysis, $\Delta Borg_{dysp,iso}$ correlated significantly with ΔT_{lim} (r_s=-0.483), a relationship which has been well reported elsewhere[3,255,279,280]. $\Delta Borg_{dysp,iso}$ was also related to ΔRR_{iso} and $\Delta V_{E,iso}$, the biggest fall in Borg scores therefore again occurring in subjects with the smallest increases or even decreases in $V_{E,iso}$.

ΔT_{lim} had a significant negative correlation with $\Delta VCO_{2,iso}$ (r_s=-0.332), ΔRR_{iso} (r_s=-0.367), $\Delta V_{E,iso}$ (r_s=-0.432), $\Delta V_E/VO_2$ (r_s=-0.427) and $\Delta V_E/VCO_2$ (r_s=-0.325). The relationship between ΔT_{lim} and $\Delta V_{E,iso}$ is shown graphically in Figure 3.1.4. This demonstrates that subjects who were able to exercise for longer following bronchodilator were predominantly those who had no increase in $V_{E,iso}$. Conversely, subjects who showed no increase in T_{lim} following bronchodilator tended to have increased $V_{E,iso}$. This finding perhaps adds a further

explanation to the debate as to why bronchodilators do not universally enhance exercise performance in COPD. Any improvement in ventilatory mechanics gained from bronchodilator may be lost due to an increase in ventilatory requirements possibly due to increased ventilation–perfusion mismatch.

Figure 3.1.4. Relationship between isotime values of ΔV_E and ΔT_{lim}



Since bronchodilators are thought to improve exercise ability by improving respiratory mechanics (by reducing dynamic hyperinflation or airway resistance) and hence increasing ventilatory capacity[198,279,280], it was surprising to find no relationship between $\Delta V_{E,end}$ and ΔT_{lim} despite an increase in both with bronchodilator therapy. There are several factors which could diminish the ability of this study to prove an association, namely:

- Improved ventilatory capacity due to bronchodilators may not translate into improved exercise performance if there is a simultaneous worsening of gas exchange[317] or suppression of peripheral muscle function[318].
- Not all subjects who show a detectable change in resting pulmonary function with bronchodilators can convert this into an improvement in exercise capacity, the postulated reason being the manner in which the chest wall muscles adapt to the changes produced by the bronchodilator[285]. More severely affected subjects who had resting hyperinflation and who permitted dynamic hyperinflation were more likely to experience benefit from bronchodilators.

- Ventilatory capacity was not the limiting physiological component in a proportion of our subjects[284].
- T_{lim} has poor reproducibility. Its coefficient of variation has been estimated as 34%, compared with IC (20%) and $V_{E,end}$ (15%)[255] and, when measured as a change, the size of the error is compounded.

None of the changes in resting pulmonary function variables were associated with ΔT_{lim} (the measure of exercise capacity) or $\Delta Borg_{dysp,iso}$ (the measure of breathlessness), which is discrepant with earlier studies that were able to show a correlation, albeit weak, between ΔT_{lim} or $\Delta Borg_{dysp,iso}$ and ΔIC[3]. However, it does fit with the finding of lack of association between $\Delta V_{E,end}$ and ΔT_{lim} and suggests again that the mechanical improvement induced by bronchodilators was not translated into improved exercise capacity. Alternatively, this may have been due to differences in study design (O'Donnell[3] had twice the number of exercise tests per subject in his study), severity of airways obstruction (less in our study) or subject heterogeneity (in our study the entry criteria allowed any cause of airways obstruction). If a subgroup analysis were performed including only the subjects in our study who had COPD (n=36), the correlation coefficient between ΔT_{lim} and ΔIC increased (r=0.317) but did not become significant. A further point is that the relationship between IC and T_{lim} may only exist for those subjects whose tidal breathing is limited by flow limitation[282] and this was not required for entry into this study[281].

Association of resting pulmonary function variables with $V_{E,end}$ have rarely been reported in the context of cycle endurance and bronchodilator reversibility tests[280]. In this study, changes in $V_{E,end}$ were significantly associated with changes in IC and resistive parameters such as R_{aw}, $1/sG_{aw}$ and $X_{rs,insp}$. Notably, there was no association with changes in FEV_1. This suggests that the increase in ventilatory capacity during exercise produced by bronchodilators can be predicted to some extent from resting measurements of resistance or IC but not FEV_1.

In terms of a measurable change post-bronchodilator, no single variable was any more sensitive than FEV_1 in our cohort when significant change was defined by placebo response. However, each test identified a different but overlapping set of responders and combining parameters lead to a 50% increase in the number of responders identified. Between-study comparison of this outcome is difficult as there is no gold standard of reversibility with which

to compare and studies have used different definitions of a significant response in different populations[3,216,314].

Conclusions

- Bronchodilator produced measurable changes in plethysmography, oscillometry and exercise test parameters. Changes in RWV and PTT were non-significant or small relative to the errors in the measurement.
- Changes in resting IC and resistive parameters including $X_{rs,insp}$ were significantly associated with changes in $V_{E,end}$ whereas changes in FEV_1 were not. However, neither changes in resting pulmonary function nor changes in $V_{E,end}$ were associated with changes in T_{lim} suggesting that the increased ventilatory capacity predicted by these changes in resting pulmonary function tests may not necessarily translate into improved exercise tolerance.
- Of the oscillometry variables, $\Delta X_{rs,insp}$ was most strongly associated with $\Delta V_{E,end}$, consolidating the suggestion that it is the optimum oscillometry choice for reflecting resistive change. Estimation of work of breathing by combination of $X_{rs,insp}$ and flow data conferred no advantage over the use of $X_{rs,insp}$ alone.

3.2 Longitudinal Predictors of Progression in Interstitial Lung Disease

Introduction

The term interstitial lung disease (ILD) encompasses a range of heterogeneous conditions with more than 200 subtypes characterised by involvement of the pulmonary parenchyma. The commonest manifestations of this disease class are idiopathic pulmonary fibrosis and sarcoidosis[319-321]. The different forms of ILD broadly share a common physiological defect[322] typified by restricted lung volumes and impaired diffusing capacity. Lung compliance and gas exchange are also impaired. On exercise testing the characteristic rapid, shallow breathing pattern becomes more prominent as larger minute ventilation is achieved by increased respiratory frequency and there is usually arterial desaturation and a widened alveolar-arterial O_2 gradient.

There are differences in pathophysiological detail between the various subtypes of ILD[322]. A mixed obstructive-restrictive defect is seen in sarcoidosis, hypersensitivity pneumonitis and Langerhan's cell histiocytosis. There is a disproportionate reduction in diffusing capacity in idiopathic pulmonary fibrosis (IPF) compared with sarcoidosis and asbestosis. Residual volume is often elevated in asbestosis, silicosis and hypersensitivity pneumonitis but reduced in IPF. There is a greater degree of arterial desaturation during exercise in IPF than sarcoidosis or fibrosing alveolitis complicating scleroderma. These differences are sufficiently distinct to make it difficult to generalise the conclusions from a physiological study of one subtype to another whilst at the same time the considerable overlap in results renders the standard pulmonary function tests relatively poor at differentiating between them. This has been compounded by changes in pathological classification over the years[323].

The optimum approach for monitoring progression in ILD is still not clear. Interest has focussed on symptom questionnaires, imaging, physiological tests both resting and during exercise, and composite scores which include a combination of these elements. There is most evidence for IPF.

Since the 1970s many studies have demonstrated a link between baseline physiological impairment and increased mortality. The importance of reduced FVC[324-328] and T_{LCO}[325,328-333] values have received most support although changes in FEV_1/FVC[334] and TLC[335,336] have also been studied. Resting gas exchange (in the form of P_aO_2 and $P_{(A-a)}O_2$) has shown variable results with some studies showing an association with survival[337,338] and some not[336]. Transfer coefficient (K_{CO})[332,336,337] did not prove useful. There are fewer studies looking at the prognostic significance of longitudinal trends. Studies have not in general been in favour of $P_{(A-a)}O_2$[2,338-340] but have confirmed the significance of changes in FVC[2,333,338,340,341] and T_{LCO}[328,338,340,342], the timescales required to detect change being 6 months or 1 year. It has been of particular interest to see that, although histological differentiation between usual interstitial pneumonitis and non-specific interstitial pneumonitis has been important at baseline to predict prognosis, at later assessment time points this became irrelevant, with trends in pulmonary function variables being the only important prognostic determinants[328,333]. Recently in a review of the available data it was proposed that T_{LCO} was the optimum measurement for quantifying impairment at baseline and fall in FVC was optimum for indicating progression of disease[343].

The evidence for the prognostic benefit of exercise testing in IPF is less well developed. Parameters such as changes in gas exchange and $P_{(A-a)}O_2$ during exercise have been shown to correlate with surrogate markers of disease progression. Fulmer[344] found that the change in P_aO_2 during exercise correlated with the degree of fibrosis on lung biopsy and Agusti[339] showed that the change in $P_{(A-a)}O_2$ during exercise at baseline correlated with increase in its resting value at 20 months. One longitudinal study was able to show an association between increased $P_{(A-a)}O_2$ and decreased survival[338] but in general this variable has not been favoured because of poor reproducibility compared with FVC and T_{LCO}[2]. Data linking parameters from incremental cycle exercise tests to survival is contradictory. These studies have concentrated on gas exchange variables during exercise such as P_aO_2 and $P_{(A-a)}O_2$ at peak exercise and the ratio of change in P_aO_2 to change in oxygen consumption (VO_2). Some[337,338,345] have found value in these variables whereas others[336,345,346] have not. Moreover, gas exchange variables have poorer reproducibility than VC and T_{LCO}[2]. Other forms of exercise test have been evaluated. Two studies looking at fixed time walking tests[347,348] both concluded that desaturation during the test predicted survival with the later study also suggesting that walk distance was of prognostic value. Of these two outcome variables, walk distance has been shown to have superior reproducibility[349]. Data on incremental shuttle walk tests has been

published in IPF patients, with correlation observed between performance and T_{LCO}[350], but there is no information on its ability to predict survival as yet. The utility of endurance exercise testing in IPF has not been described.

Cross-sectional studies of dyspnoea scales and instruments to measure HRQOL have been performed in IPF[351-359]. These have demonstrated that subjects with IPF have measurably worse HRQOL than controls and that the degree of deterioration in HRQOL correlates weakly with pulmonary function tests but more strongly with dyspnoea. One study has demonstrated that changes in dyspnoea measured by the CRP dyspnoea scale over 6 months and 1 year predict survival[338] but there have been no longitudinal studies in IPF comparing HRQOL data with survival. Three HRQOL instruments have principally been used, namely SF-36, SGRQ and WHO Quality of Life 100 Item Instrument (WHOQOL-100)[359].

Two scoring systems have been developed to provide a composite outcome measure in IPF, the Composite Physiologic Index (CPI) and the Clinical-Radiologic-Physiologic (CRP) Score. The CPI was derived by creating a prediction equation for disease extent on CT scan from pulmonary function results (% predicted T_{LCO}, FVC and FEV_1)[360] and has been shown to predict mortality both from baseline values and longitudinal trend[328,360]. The CRP score has already undergone one revision and is an older and more complicated amalgam of variables, including in the more modern version: age, smoking history, presence of clubbing, radiological appearance, presence of pulmonary hypertension, TLC and P_aO2 on exercise[213,337]. It has also been shown to predict survival.

There is less evidence available on the usefulness of physiological measures as prognostic indicators in other forms of ILD. As the various subtypes differ in pathology, baseline physiology (described above), natural history and responsiveness to therapy, the generalisation of the above data for IPF to other forms of ILD is speculative.

The effect of ILD on lung parenchyma should be to increase its elastance and this has been confirmed in many cross-sectional studies[238,239,245,246,344,361-366]. Several forms of ILD have been evaluated in this way ranging from IPF[344,366,367] to hypersensitivity pneumonitis[362,368], sarcoidosis[369-371], pulmonary fibrosis associated with connective tissue disease[372,373] and asbestosis[374]. Studies evaluating serial changes are rare but have been performed, largely in children[375,376] and sarcoidosis[371,377-380]. There have been no systematic studies looking at the

link between elastance and survival, the closest being Cherniack[337] who showed a weak association between lung mechanics and survival on univariate analysis. There are studies which link changes in elastance with degree of histological abnormality[246,344,381] and some data which suggest elastance may be a sensitive marker of early disease[245,382]. Some studies show a change in elastance following treatment[373,383] but others especially in sarcoidosis do not confirm this[377-380]. The major barrier preventing longitudinal elastance data on all patients with ILD is the invasive nature of the measurement which requires oesophageal manometry. There have been some attempts to evaluate non-invasive techniques to estimate elastance in ILD[161,165] but none have progressed beyond pilot studies.

Aim

The aim of this study was to explore the potential of non-invasive E_{rs} and WOB_{elas} measurements (described in Chapter 1.2) to predict progression or survival in ILD compared with conventional pulmonary function tests, exercise tests, symptoms and HRQOL.

Methods

Subjects

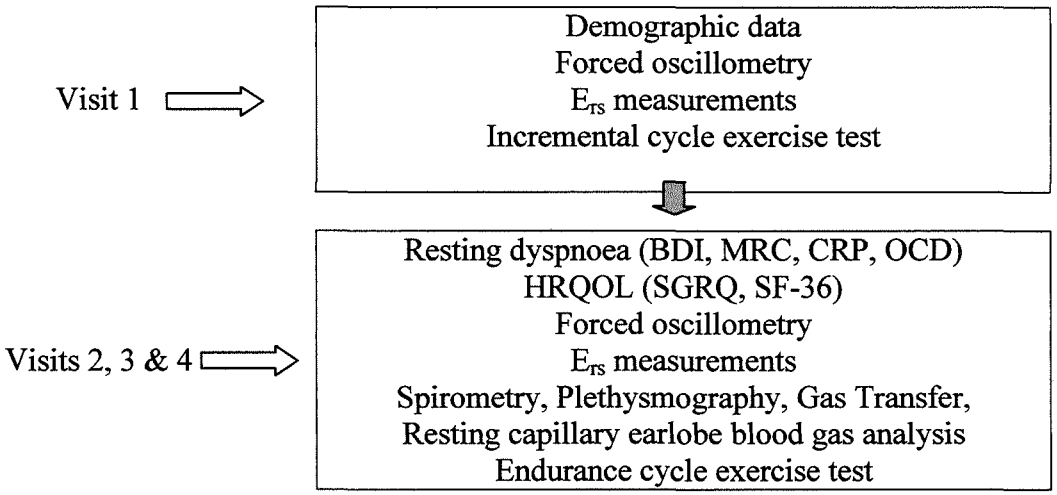
All patients with a diagnosis of ILD attending the respiratory clinic at GRI from November 2001 to July 2002 were approached to take part in the study. Subjects unable to perform a cycle exercise test were excluded. Of 68 patients approached, 23 consented and were enrolled. All of these had CT scan evidence of diffuse parenchymal lung disease.

Study Design

This was a longitudinal observational study (Figure 3.2.1). On visit 1, forced oscillometry and non-invasive E_{rs} measurements were performed as described in Chapter 1.2. The subjects also underwent incremental cycle exercise test to establish peak WR and familiarity with this

modality of exercise testing. The detailed description of all conventional physiological tests is given in Chapter 1.3.

Figure 3.2.1. Study protocol.



Visit 2 occurred within one week but greater than two days following visit 1. Its aim was to establish baseline values for the outcome parameters. The subjects completed dyspnoea and HRQOL questionnaires. Forced oscillometry and E_{rs} measurements were repeated to provide reproducibility data. Then spirometry (FEV_1), plethysmography (VC, TLC, RV, IC, R_{aw}, sG_{aw}), gas transfer (T_{LCO}) and capillary earlobe blood gas measurements (P_aO_2, P_aCO_2, $P_{(A-a)}O_2$) were performed. The final procedure was an endurance cycle exercise test. After a period of rest and then unloaded cycling, the subjects cycled at a workload of 70% of that achieved in their initial incremental cycle exercise test. During the test, measurements were taken every minute of Borg score and transcutaneous blood gases ($P_{tc}O_2$ and $P_{tc}CO_2$). Visits 3 and 4 occurred at 6 months and 1 year and were identical to visit 2. The aim of these visits was to determine whether the condition had progressed.

All operators were blinded to the results of earlier tests. Subjects were asked to avoid major physical exertion on the day of investigation. Compliance with this request was ascertained verbally on the day of the visit. For each subject the tests were performed at the same time of day.

Analytical Approach

The ideal method for assessing whether a new test is sensitive at detecting disease progression in ILD is to use survival as the outcome measure. When this study was initially designed, it was considered that survival analysis would not be possible because of low subject numbers, low mortality and short duration. Consequently, it was planned to use a surrogate indicator or progression score (Table 3.2.1) to classify the subjects into three groups, those with (1) "progressive", (2) "stable" or (3) "improved" disease. The inclusion of the elements making up this score were defined a priori. At the time of analysis of the study it became clear that three to four year survival data (all cause mortality) were available for the subjects. The analysis planned for the progression score was therefore repeated with the subjects divided into survivors and non-survivors with survival status determined at the beginning of January 2006.

Progression Score

Subjects were assigned a progression score derived objectively from the results of dyspnoea scales, HRQOL instruments, resting pulmonary function and exercise performance. A progression score of –2 or less was interpreted as indicating "progressive", a score of +2 or more "improved" and –1 to +1 "stable" disease. A detailed description of the score is shown in Table 3.2.1.

Sample Size

No repeatability data on non-invasive E_{rs} and WOB_{elas} measurements were available a priori on which to base a power calculation. It was anticipated that recruitment figures would be relatively modest given the size and morbidity of the ILD population attending the clinics. It was therefore decided to approach the entire subject population and view the study as a pilot on which to base a larger or longer study if positive.

Table 3.2.1. Details of derivation of progression score.

Score Component	Progression Score
1. Symptom questionnaires Each subject completed 4 dyspnoea scales (MRC, CRP, OCD, BDI) at 3 time points (0, 6, 12 months). The results for each questionnaire were scored by comparing values at 0 and 12 months. If dyspnoea had increased, the score was –1, if no change 0 and if decreased +1. The 4 scores were summed and the results converted to an overall progression score as follows:-	-1 to +1

Dyspnoea Scale Score	Progression Score
-2 to –4	-1
-1 to +1	0
+2 to +4	+1

2. HRQOL instruments Each subject completed 2 HRQOL questionnaires (SGRQ, SF-36) at the 3 time points. Again results at 0 and 12 months were compared. If both questionnaires were concordant in showing an increase or decrease in HRQOL, a progression score of +1 or –1 respectively was assigned. Otherwise the score was 0.	-1 to +1
3. Vital capacity, VC Comparison was made between 0 and 12 month results	
≥ 10% increase^{+}	+1
≥ 10% decrease^{+}	-1
otherwise	0
4. Gas transfer, T_{LCO} Comparison was made between 0 and 12 month results	
≥ 15% increase^{+}	+1
≥ 15% decrease^{+}	-1
otherwise	0
5. Exercise performance Endurance exercise time was examined at all 3 time points and scored as follows:-	
Monotonic increase over 3 time points	+1
Monotonic decrease over 3 time points	-1
Other	0
Total Progression Score	-5 to +5

$^{+}$ *denominator is the average value at 0 and 12 months*

Statistical Methods

Baseline results were summarised as mean (SD). Between day reproducibility of the E_{rs} and WOB_{elas} results was assessed using coefficient of variation and intraclass correlation coefficient as described in Chapter 3.1. Change data for the progression score analysis are shown as mean. Difference in mean values between the three classes of disease progression and evidence of linear trend was assessed using one way ANOVA. This analysis was repeated using a non-parametric form of the analysis, the Kruskal-Wallis Test. Change data for the survival analysis are shown as median (range) and difference between the two survival groups was assessed using the Mann Whitney U test. The relative ability of individual variables to predict progression score or survival was assessed by area under the curve (AUC) of receiver operating characteristic (ROC) curves and (for survival) by univariate and multivariate Cox proportional hazards regression. The ability of the progression score to predict survival was tested using Kaplan-Meier analysis with the logrank test. The level of statistical significance was taken as 0.05. No compensation for multiple comparisons (such as the Bonferroni method) has been explicitly applied and this should be taken into consideration when interpreting the significance of results. All statistics where performed with Statview v 5.0.1 (SAS Institute Inc.) or SPSS v 12.0.1 (SPSS Inc.).

Results

Baseline Characteristics

The disease characteristics of the subjects enrolled in the study are shown in Table 3.2.2. Follow-up was complete except for two subjects who did not attend for Visit 4. One of these developed leukaemia and the other was lost to follow-up. Exercise test data were obtained at all visits in 21 of these patients. One patient was unable to exercise at any visit because of lower limb arthritis and one patient could not exercise at Visit 4 because of a displaced femoral head.

Table 3.2.2. Characteristics of subjects.

Patient No	Sex	Age	Diagnosis	Biopsy	Duration of Symptoms (Years)	Smoking History	
						Status	Pack years
1	M	65	IPF[1]	NO	2	Current	40
2	F	54	IPF	YES	3	Ex	15
3	M	68	IPF	NO	3	Never	-
4	F	58	IPF	YES	5	Never	-
5	M	50	IPF	NO	2	Ex	45
6	F	59	IPF	NO	9	Current	50
7	M	76	IPF	NO	1	Ex	15
8	M	65	IPF	NO	21	Current	30
9	F	71	IPF	NO	1	Ex	50
10	M	74	IPF	NO	2	Ex	70
11	F	51	IPF	YES	1	Ex	10
12	F	56	HP[2]	YES	1	Never	-
13	M	72	HP	YES	4	Never	-
14	M	70	HP	YES	3	Never	-
15	F	65	CTD[3] associated	YES	4	Never	-
16	F	66	CTD associated	NO	3	Never	-
17	F	64	CTD associated	NO	5	Ex	5
18	F	66	Sarcoidosis	YES	4	Never	-
19	M	63	Sarcoidosis	YES	1	Ex	0.5
20	M	66	Drug toxicity[4]	NO	2	Current	24
21	F	67	Drug toxicity[5]	NO	1	Ex	25
22	M	60	Silicosis	YES	18	Current	80
23	M	52	Post-BMT[6]	NO	1	Never	-

[1] Idiopathic pulmonary fibrosis
[2] Hypersensitivity pneumonitis
[3] Connective tissue disease
[4] Bleomycin
[5] Nitrofurantoin
[6] Bone marrow transplant

Baseline conventional pulmonary function tests (Table 3.2.3) showed that the subjects as a group had the characteristics of ILD. There was evidence of a restrictive lung defect with low lung volumes (VC, FEV_1, RV, TLC and IC). Diffusing capacity (T_{LCO}) was markedly impaired. R_{aw} was elevated (normal <0.2) whereas sG_{aw} was normal (>1.1) which is consistent with elevated resistance due to low lung volumes. Gas exchange showed a mild hypoxia with elevated resting $P_{(A-a)}O_2$ (normal <2.9 kPa[195]). Baseline results for E_{rs} and WOB_{elas} are also shown in Table 3.2.3.

Incremental cycle exercise tests (Table 3.2.4) showed a reduced exercise capacity and $VO_{2,peak}$. There was a greater than predicted heart rate reserve but ventilation reached the predicted breathing reserve (normal $V_{E,peak}$ – 72% ± 15%[198]) suggesting a degree of ventilatory limitation. Breathing frequency at end exercise was higher than the COPD subjects in Chapter 3.1 (mean values 41 vs 33 breaths.min^{-1} respectively). AT, O_2 pulse and $\Delta VO_2/\Delta WR$ were all reduced suggesting an element of circulatory limitation[198]. At end exercise $P_{tc}O_2$ decreased and both $P_{(A-tc)}O_2$ and V_D/V_T increased (normal V_D/V_T <0.30[198]). This pattern of mixed circulatory, gas exchange and ventilatory impairment is consistent with ILD[198,322,384].

The scores from the dyspnoea scales (Table 3.2.5) showed that the subjects had a significant level of symptoms as found in ILD in other studies[357,385]. HRQOL was also impaired. Compared with the values from recent studies using SF-36 and SGRQ[359], the mean HRQOL of our subjects was markedly worse than normals (see Chapter 1.3) and slightly worse than other ILD cohorts. This suggested that we may have enrolled a more severely affected study group.

Table 3.2.3. Baseline characteristics of study patients: resting pulmonary function tests including E_{rs} and WOB_{elas}.

		Mean (SD) (n=23)
Sex (male : female)		11:12
Age (years)		63.4 (7.31)
Weight (kg)		76.5 (16.2)
Height (m)		1.64 (0.09)
BMI ($kg.m^{-2}$)		28.3 (5.13)
Smoking history		
- **ex/current smokers : non-smokers**		14:9
- **pack years**		32.8 (24.1)
Spirometry / Plethysmography / Gas Transfer		
VC	**L**	2.68 (0.70)
	% pred	90.1 (20.8)
FEV_1	**L**	1.97 (0.50)
	% pred	81.5 (17.4)
FEV_1/VC	**%**	74.0 (8.1)
	% pred	96.7 (10.8)
RV	**L**	1.68 (0.45)
	% pred	81.2 (22.7)
TLC	**L**	4.36 (0.92)
	% pred	80.9 (15.9)
IC	**L**	1.88 (0.51)
	% pred	76.1 (21.3)
Raw	**$kPa.s.L^{-1}$**	0.23 (0.07)
sGaw	**$L^2.kPa^{-1}.s^{-1}$**	1.78 (0.60)
T_{LCO}	**$ml.min^{-1}.kPa^{-1}$**	3.93 (1.56)
	% pred	50.1 (17.0)
Gas exchange at rest		
P_aO_2	**kPa**	9.91 (1.40)
P_aCO_2	**kPa**	4.87 (0.60)
$P_{(A-a)}O_2$	**kPa**	4.52 (1.49)
E_{rs} / WOB_{elas}		
$E_{rs,NIV}$	**$kPa.L^{-1}$**	2.68 (1.09)
$WOB_{elas,NIV}$	**$J.min^{-1}$**	9.27 (4.26)
	$J.L^{-1}$	0.737 (0.262)
$E_{rs,CPAP}$	**$kPa.L^{-1}$**	1.54 (0.93)
$WOB_{elas,CPAP}$	**$J.min^{-1}$**	5.98 (4.68)
	$J.L^{-1}$	0.444 (0.230)

Table 3.2.4. Baseline characteristics of study patients: incremental and endurance cycle exercise tests.

		Mean (SD) (n=23)	
Incremental cycle exercise test			
Maximum WR	**W**	64 (35)	
$VO_{2,peak}$	**$L.min^{-1}$**	0.93 (0.32)	
	% pred	61 (23)	
HR_{peak}	**min^{-1}**	128 (19)	
HRR	**min^{-1}**	28 (19)	
$V_{E,peak}$	**$L.min^{-1}$**	52.5 (16.0)	
	% MVV	68 (16)	
RR_{peak}	**min^{-1}**	41(10)	
$V_{T,peak}$	**L**	1.29 (0.53)	
AT	**% pred $VO_{2,peak}$**	37 (15)	
O_2 $pulse_{peak}$	**% pred**	74 (25)	
$\Delta VO_2/\Delta WR$	**$ml.min^{-1}.W^{-1}$**	8.33 (2.82)	
$\Delta P_{tc}O_{2,peak}$	**kPa**	-1.15 (1.38)	
$\Delta P_{tc}CO_{2,peak}$	**kPa**	-0.24 (0.54)	
$P_{(A-tc)}O_{2,peak}$	**kPa**	6.90 (2.25)	
$V_D/V_{T,rest}$		0.57 (0.10)	
$V_D/V_{T,peak}$		0.42 (0.13)	
Endurance cycle exercise test			
T_{lim}	**min**	8.9 (3.6)	
		Isotime	**End-exercise**
VO_2	**$L.min^{-1}$**	0.83 (0.32)	0.95 (0.33)
HR	**min^{-1}**	116 (31)	125 (21)
RR	**min^{-1}**	38 (9)	40 (8)
V_T	**L**	1.23 (0.50)	1.21 (0.47)
V_E	**$L.min^{-1}$**	44.2 (15.9)	46.5 (15.6)
$Borg_{dysp}$		4.9 (2.0)	7.3 (2.3)
$Borg_{leg}$		5.9 (2.2)	7.8 (2.4)
V_E/VO_2		55.7 (13.6)	59.1 (18.4)
V_E/VCO_2		44.7 (9.5)	46.3 (11.1)
$\Delta P_{tc}O_2$,	**kPa**	-0.88 (1.29)	-1.18 (1.40)
$\Delta P_{tc}CO_2$	**kPa**	-0.13 (0.50)	-0.23 (0.51)
$P_{(A-tc)}O_2$	**kPa**	6.25 (2.05)	6.67 (2.42)
V_D/V_T		0.43 (0.13)	0.41 (0.20)

Table 3.2.5. Baseline characteristics of study patients: symptom and HRQOL instruments.

	Mean (SD) (n=23)
Dyspnoea Scales	
MRC	2.87 (0.97)
CRP	7.48 (4.52)
OCD	0.57 (0.25
BDI	5.7 (3.1)
HRQOL	
SGRQ	
Symptoms	57.0 (25.9)
Activities	65.8 (25.2)
Impacts	37.7 (21.2)
Total Score	49.8 (21.2)
SF-36	
Physical functioning	43.0 (28.5)
Physical role	34.8 (44.4)
Bodily pain	66.7 (28.6)
General health	43.6 (22.9)
Vitality	42.6 (22.6)
Social functioning	65.7 (27.8)
Emotional role	43.5 (45.4)
Mental health	68.3 (15.3)
Summary scores	
PCS	30.0 (14.4)
MCS	45.9 (10.3)

Reproducibility

Reproducibility of the E_{rs} and WOB_{elas} results are shown in Table 3.2.6. Results for the NIV method were poor and these were not analysed further. Repeatability for the CPAP method was more acceptable.

Disease Progression

The results of the algorithm for defining disease progression are shown in Table 3.2.7. Nine of the eleven patients with IPF were classed as either "stable" or "progressive". Of the two

with IPF who appeared to improve, neither had had a biopsy to confirm the diagnosis and the possibility exists that they had been misclassified as IPF. Of the 7 subjects with "progressive" disease, 3 showed worsening pulmonary function tests (1 VC and T_{LCO}, 2 T_{LCO} alone), 4 had deteriorating exercise capacity, 4 deteriorating HRQOL and all 7 worsening dyspnoea scores.

Table 3.2.6. Reproducibility analysis. E_{rs} and oscillometry data from visits 1 and 2.

	Mean		Coefficient of Variation (%)	Intraclass R
	Visit 1	Visit 2		
Pulse/CPAP measurements				
$E_{rs,NIV}$ (kPa.L^{-1})	2.80	2.80	29.3	0.692
$WOB_{elas,NIV}$ (J.L^{-1})	0.810	0.739	76.1	0.490
(J.min^{-1})	10.8	8.82	116	0.434
$E_{rs,CPAP}$ (kPa.L^{-1})	1.47	1.62	17.3	0.913
$WOB_{elas,CPAP}$ (J.L^{-1})	0.450	0.432	16.4	0.786
(J.min^{-1})	6.21	5.38	12.8	0.792

Table 3.2.7. Results of subdivision of stable patients into "progressive", "stable" or "improved" disease.

	Progressive	Stable	Improved
Diagnoses	IPF – 4	IPF – 5	IPF – 2
	HP – 2	Silicosis - 1	HP - 1
	Sarcoidosis - 1	Drug toxicity - 1	Post BMT - 1
		CTD associated - 1	Sarcoidosis - 1
			Drug toxicity - 1
			CTD associated - 2
Total	7	8	8

Variation of Physiological Variables with Disease Progression Status

The analysis in Tables 3.2.8 to 3.2.10 showed whether the change in physiological variables over twelve months differed between the subjects when grouped by status of disease progression. Only the ANOVA results are shown as the non-parametric analysis produced the same distribution of significance of results. Since T_{LCO}, VC, T_{lim}, dyspnoea and HRQOL

were part of the algorithm used to define the presence or absence of disease progression, it would be expected for them to show significant difference and linear trend. The size of the change in SGRQ exceeded the recognised minimum clinically important difference.

Disease progression was associated with longitudinal trends in exercise test variables other than T_{lim} including

- rest variables: increasing $P_{(A-a)}O_2$, RR and V_E
- isotime variables: increase in RR, V_E, R and ventilatory equivalents
- reduction in peak VO_2 but no other end-exercise variables.

Physiologically these changes reflect worsening efficiency of ventilation and gas exchange as the subject's condition deteriorates. There was a strongly significant difference and linear trend across the patients groups for increasing $E_{rs,CPAP}$ and $WOB_{elas,CPAP}$ with "progressive" disease. The distribution of results for some of the significant variables is illustrated in Figure 3.2.2.

Finally, dividing the subjects into two groups either showing progression or non-progression, ROC curves were constructed and the AUC calculated (Table 3.2.11). $E_{rs,CPAP}$ and $WOB_{elas,CPAP}$ performed better than conventional pulmonary function and exercise testing, which was surprising when it was considered that this analysis was biased in favour of the latter variables which were used as part of the method for defining disease progression. ROC curves for $E_{rs,CPAP}$, VC, T_{lim} and CRP score are shown in Figure 3.2.3.

Table 3.2.8. Change in physiological results over 12 months grouped by progression score. Results of one way ANOVA on resting pulmonary function tests.
Significance testing was performed both for difference between means and linear trend.

		Change over 12 months			Difference	Linear trend
		Progressed (n=7)	Stable (n=8)	Improved (n=8)	p-value	p-value
Spirometry / Plethysmography / Gas Transfer						
VC	**L**	-0.053	0.016	0.213	NS (0.10)	**0.04**
	% pred	-2.071	2.014	7.252	NS (0.10)	**0.04**
FEV_1	**L**	-0.004	0.041	0.095	NS	NS
	% pred	0.472	3.070	4.042	NS	NS
FEV_1/VC	**%**	2.143	1.250	-2.375	NS	NS
	% pred	3.054	1.930	2.791	NS	NS
RV	**L**	-0.080	0.114	-0.042	NS	NS
	% pred	-4.500	4.804	-2.914	NS	NS
TLC	**L**	-0.136	0.126	0.168	NS	NS
	% pred	-2.795	2.646	2.915	NS	NS
IC	**L**	-0.121	-0.060	0.212	NS	NS
	% pred	-5.109	-1.506	10.125	NS	NS (0.10
Raw	**$kPa.s.L^{-1}$**	0.017	-0.020	0.020	NS	NS
sGaw	**$L^2.kPa^{-1}.s^{-1}$**	-0.101	0.139	-0.314	NS	NS
T_{LCO}	**$ml.min^{-1}.kPa^{-1}$**	-0.286	-0.500	0.850	**0.007**	**0.01**
	% pred	-3.687	-6.591	12.325	**0.007**	**0.01**
Resting Gas Exchange						
P_aO_2	**kPa**	-0.556	-0.309	-0.010	NS	NS
P_aCO_2	**kPa**	0.059	-0.009	-0.087	NS	NS
$P_{(A-a)}O_2$	**kPa**	1.263	0.247	-0.086	**0.049**	**0.02**
E_{rs} / WOB_{elas}						
$E_{rs,CPAP}$	**$kPa.L^{-1}$**	0.598	-0.474	-0.203	**0.006**	**0.01**
$WOB_{elas,CPAP}$	**$J.min^{-1}$**	3.626	-1.800	-1.313	**0.02**	**0.02**
	$J.L^{-1}$	0.173	-0.097	-0.071	**0.007**	**0.007**

Table 3.2.9. Change in physiological results over 12 months grouped by progression score. Results of one way ANOVA on exercise tests.
Significance testing was performed both for difference between means and linear trend.

		Change over 12 months			Difference	Linear trend
		Progressed (n=7)	Stable (n=8)	Improved (n=8)	p-value	p-value
Endurance cycle exercise test						
T_{lim}	min	-1.58	1.086	3.517	NS (0.10)	**0.03**
Resting variables						
RR	min^{-1}	3.336	-1.054	-3.507	NS (0.06)	**0.02**
V_T	L	0.051	0.044	0.036	NS	NS
V_E	$L.min^{-1}$	2.861	0.130	-1.067	**0.01**	**0.004**
Isotime variables						
VO_2	$L.min^{-1}$	-0.054	-0.064	-0.027	NS (0.08)	**0.03**
HR	min^{-1}	-14.6	-0.667	-11.938	NS	NS
RR	min^{-1}	5.04	-4.429	-5.109	NS (0.06)	**0.03**
V_T	L	-0.005	-0.017	0.036	NS	NS
V_E	$L.min^{-1}$	6.18	-5.954	-3.342	NS (0.07)	NS (0.07)
R		0.233	-0.173	-0.017	**0.02**	NS (0.07)
$Borg_{dysp}$		0.571	-0.786	-0.688	NS	NS
$Borg_{leg}$		1.5	-1.786	-0.875	NS	NS
V_E/VO_2		18.18	-4.096	-4.493	**0.01**	**0.01**
V_E/VCO_2		4.22	3.378	-2.46	NS	NS (0.06)
$\Delta P_{tc}O_2$,	kPa	-0.533	-0.286	0.829	NS	NS
$\Delta P_{tc}CO_2$	kPa	0.152	0.038	-0.152	NS	NS
$P_{(A-tc)}O_2$	kPa	2.097	1.022	0.183	NS	NS
V_D/V_T		0.061	0.058	-0.059	NS	NS
$\Delta P_{tc}O_2/\Delta VO_2$	$kPa.min.L^{-1}$	-2.179	-0.717	1.581	NS	NS
End-exercise variables						
VO_{2peak}	$L.min^{-1}$	-0.172	-0.013	0.073	NS (0.07)	**0.03**
HR	min^{-1}	1.286	5.167	-23.375	NS	NS
RR	min^{-1}	1.749	-2.133	-0.569	NS	NS
V_T	L	-0.003	0.037	0.071	NS	NS
V_E	$L.min^{-1}$	2.67	-2.356	4.24	NS	NS
R		0.029	-0.119	-0.107	NS	NS
$Borg_{dysp}$		-1	-2.143	-0.5	NS	NS
$Borg_{leg}$		0	-1.286	-0.5	NS	NS
V_E/VO_2		15.469	-0.643	-1.763	NS	NS
V_E/VCO_2		3.666	4.693	-0.566	NS	NS
$\Delta P_{tc}O_2$,	kPa	-0.152	-0.229	1.2	NS	NS
$\Delta P_{tc}CO_2$	kPa	0.210	-0.095	-0.514	NS	NS
$P_{(A-tc)}O_2$	kPa	1.533	1.239	0.219	NS	NS
V_D/V_T		0.029	0.080	-0.107	NS	NS
$\Delta P_{tc}O_2/\Delta VO_2$	$kPa.min.L^{-1}$	-1.280	-0.569	1.856	NS	NS

Table 3.2.10. Change in physiological results over 12 months grouped by progression score. Results of one way ANOVA on dyspnoea scales and HRQOL instruments. Significance testing was performed both for difference between means and linear trend.

	Change over 12 months			Difference	Linear trend
	Progressed (n=7)	Stable (n=8)	Improved (n=8)	p-value	p-value
Dyspnoea scales					
MRC	0.714	0.000	-0.375	**0.03**	**0.01**
CRP	2.857	-0.250	-2.000	**0.05**	**0.02**
OCD	-0.112	0.016	-0.065	NS	NS
BDI	-1.714	0.875	1.125	NS (0.10)	NS (0.05)
HRQOL					
SGRQ					
Symptoms	2.706	-8.366	-15.258	0.35	0.15
Activities	6.550	1.794	-14.954	**<0.001**	**<0.001**
Impacts	5.742	-6.506	-12.545	NS (0.05)	**0.02**
Total	5.186	-4.048	-13.645	**0.02**	**0.005**
SF-36					
Physical functioning	-15.000	-0.625	11.875	**0.02**	**0.006**
Physical role	-3.571	-6.250	12.500	NS	NS
Bodily pain	-9.524	0.000	13.889	NS (0.08)	**0.03**
General health	-3.143	-10.375	16.875	**0.0004**	**0.003**
Vitality	0.714	5.00	16.25	NS	NS
Social functioning	-15.873	-2.778	6.944	NS	NS (0.07)
Emotional role	9.524	-8.333	29.167	NS	NS
Mental health	-2.286	-9.5	6.00	NS (0.06)	NS
Summary scores					
PCS	-6.794	-0.589	6.196	**0.02**	**0.005**
MCS	1.44	-2.971	5.974	NS	NS

Figure 3.2.2. Change over 12 months in physiological variables, symptoms and HRQOL in the patients categorised by progression score (a) T_{LCO} (b) VC (c) V_E/VO_2 (d) $E_{rs,CPAP}$ (e) $WOB_{elas,CPAP}$ ($J.min^{-1}$) (f) $WOB_{elas,CPAP}$ ($J.L^{-1}$).

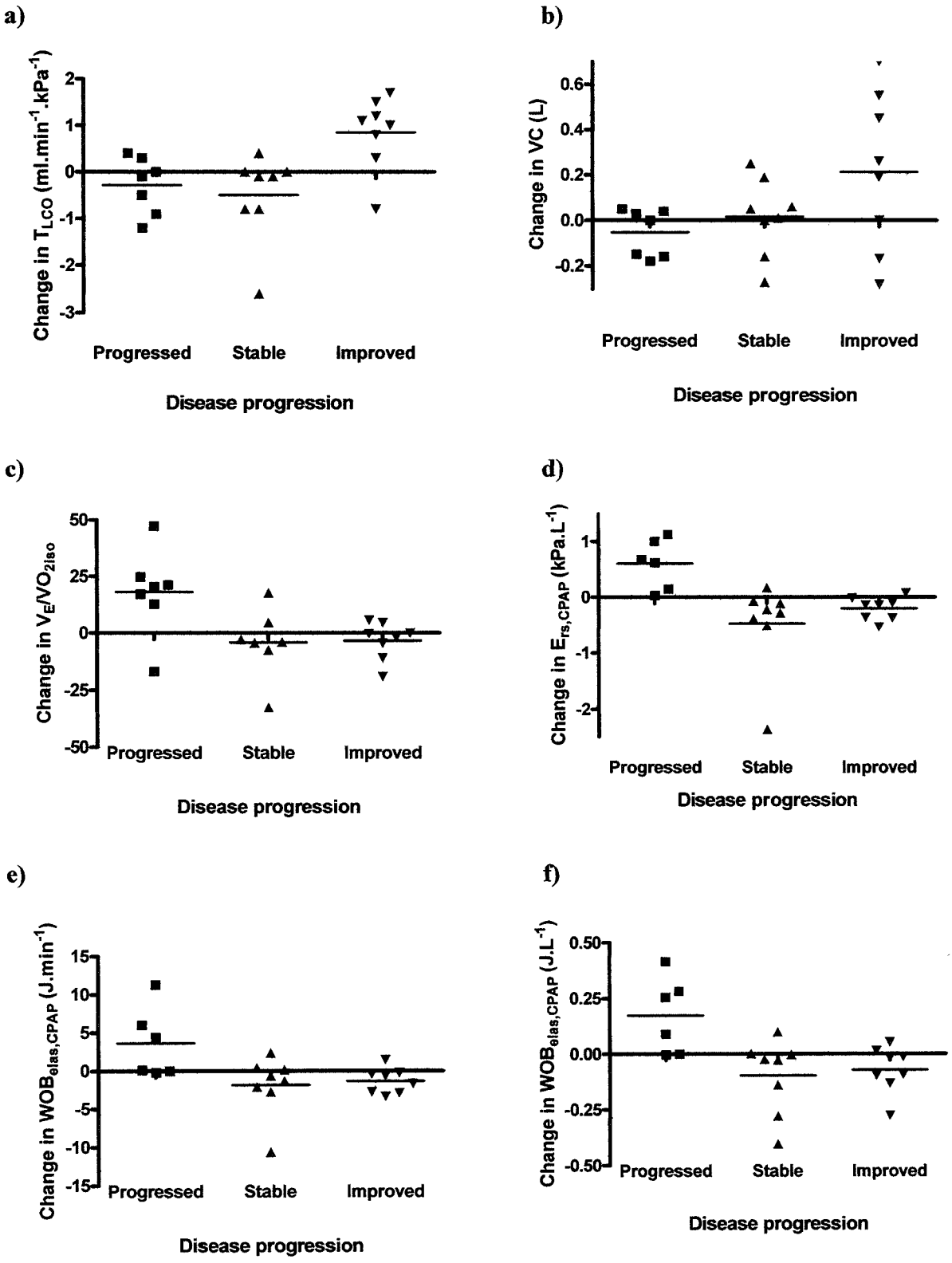
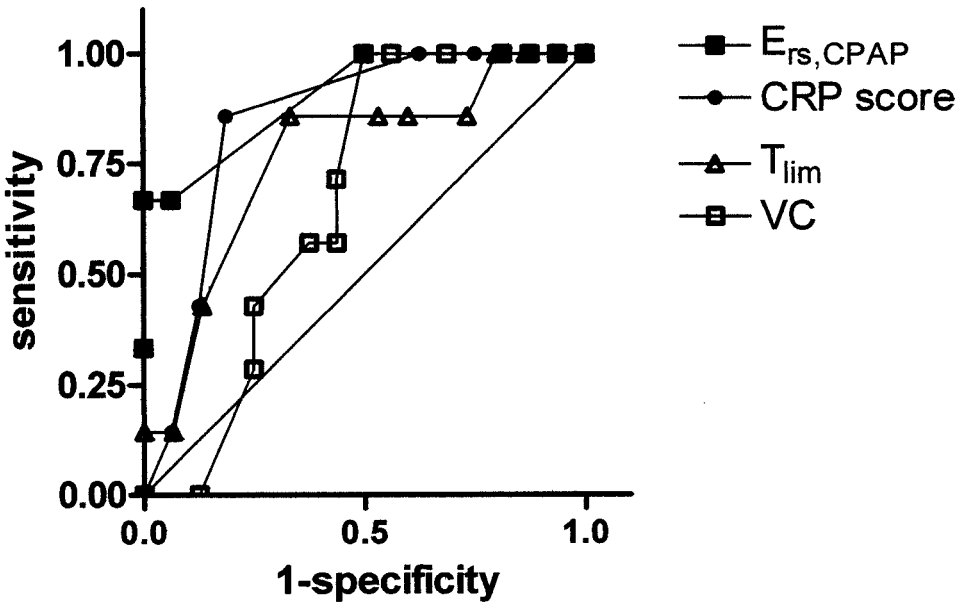


Table 3.2.11. Area under ROC curves for the progression score.

Variable	AUC
VC	0.670
T_{LCO}	0.665
T_{lim}	0.762
$P_{(A-a)}O_2$	0.804
$V_{E,rest}$	0.886
$V_E/VO_{2,iso}$	0.867
CRP	0.844
MRC	0.786
SGRQ	0.799
SF-36 PCS	0.772
$E_{rs,CPAP}$	0.906
$WOB_{elas,CPAP}$ ($J.L^{-1}$)	0.875
$WOB_{elas,CPAP}$ ($J.min^{-1}$)	0.844

Figure 3.2.3. ROC curves showing relative performance of variables for predicting progression score.



Survival Analysis

Eight of the 23 subjects had died (from any cause) by the beginning of January 2006. Difference in pulmonary function, endurance exercise test performance, symptoms, HRQOL, E_{rs} and WOB_{elas} variables between subjects who died or survived are shown in Tables 3.2.12 to 3.2.14. Baseline values, change at 6 months and change at 12 months are given. The change at 12 months is further illustrated in Figure 3.2.4 by plots of the variables showing statistically significant change. The major differences compared with the earlier similar analysis for progression score were that:-

- the changes in $E_{rs,CPAP}$ and $WOB_{elas,CPAP}$ had lost their significance
- there was a clearer pattern of change in exercise variables with significant differences in T_{lim}, isotime values of RR, V_E, R, $Borg_{dysp}$, $Borg_{leg}$, V_E/VO_2, V_E/VCO_2, $\Delta P_{tc}O_2$, $P_{(A-tc)}O_2$ and end-exercise value of V_E/VO_2 and V_E/VCO_2
- the significance of differences in dyspnoea scores weakened whereas the differences in HRQOL remained strong especially SGRQ.

ROC curves were again constructed for variables with significant 12 month changes and the AUC values are given in Table 3.2.15. The ROC curves for $V_E/VO_{2,end}$, SGRQ (Total score), VC and T_{LCO} are shown in Figure 3.2.5. To corroborate the findings of the ROC curve analysis, the ability of longitudinal changes of each variable to predict survival was further assessed using Cox proportional hazards regression. The results of univariate analysis are shown in Table 3.2.16 again restricted to variables with significant 12 month change. Multivariate analysis was also performed but this lead to no significant relationships.

According to their progression score, five of the subjects who had died were classed as having "progressive" disease and three "stable" disease. None of the "improved" group had died. Kaplan-Meier survival analysis based on these data are shown in Figure 3.2.6. The patients were placed into two groups depending on whether they had "progressive" or "stable/improved" disease on their progression score. Using the logrank test, there was a clearly significant and appropriate prognostic difference between the two groups.

Table 3.2.12. Resting pulmonary function test results over 12 months grouped by survival. Values are median (range). Significance testing was performed using the Mann Whitney U test looking at differences between the groups who died and survived at each timepoint.

		Baseline		Change over 6 months		Change over 12 months	
		Died (n=8)	Survived (n=15)	Died (n=8)	Survived (n=15)	Died (n=7)	Survived (n=14)
Spirometry / Plethysmography / Gas Transfer							
VC	**L**	2.45 (1.33 – 3.69)	2.62 (4.27 – 2.03)	-0.06 (-0.21 – 0.16)	0.02 (-0.17 – 0.34)§	-0.15 (-0.27 – 0.05)	0.12 (-0.28 – 0.70)§
	% pred	**75 (61 – 106)**	**100 (50 - 131)‡**	-3.03 (-6.84 – 8.02)	0.48 (-4.26 - 12.60)	**-1.97 (-8.64 – 0.46)**	**4.44 (-6.65 - 25.21)‡**
FEV_1	**L**	1.79 (1.18 – 2.35)	1.96 (1.52 – 3.18)	-0.04 (-0.06 – 0.27)	0.01 (-0.14 – 0.21)	-0.01 (-0.19 – 0.11)	0.04 (-0.18 – 0.47)
	% pred	**70 (54 – 98)**	**86 (51 – 123)‡**	-1.78 (-6.20 – 18.34)	-0.03 (-5.84 – 15.39)	0.247 (-8.23 – 9.66)	4.13 (-8.03 – 19.97)
FEV_1/VC	**%**	78 (53 – 89)	76 (59 – 82)	1.88(-1.61 – 12.42)	-0.94 (-4.22 – 4.67)§	**2.89 (-0.53 – 14.22)**	**-2.08 (-11.94 – 8.88)‡**
	% pred	100 (72 – 117)	99 (74 – 109)	2.63 (-2.67 – 17.98)	-1.07 (-5.24 – 5.37)	**4.18 (-1.11 – 20.71)**	**-1.60 (-15.50 – 12.11)‡**
RV	**L**	1.44 (0.95 – 2.65)	1.70 (1.10 – 2.64)	-0.04 (-0.43 - 0.16)	0.01 (-0.41 – 0.25)	0.050 (-0.84 – 0.50)	-0.04 (-0.37 – 0.40)
	% pred	72 (37 – 105)	83 (60 – 129)§	-2.12 (-16.98 – 6.60)	0.43 (-19.35 – 13.94)	0.60 (-33.79 – 18.12)	-2.46 (-17.91 – 21.07)
TLC	**L**	3.89 (2.75 – 5.62)	4.42 (3.34 – 6.11)	-0.05 (-0.58 – 0.22)	-0.01 (-0.28 – 0.56)	0.00 (-0.85 – 0.55)	0.09 (-0.53-0.78)
	% pred	**72 (48 – 83)**	**86 (52 – 111)‡**	-2.55 (-8.12 – 6.14)	-0.22 (-5.59 – 11.91)	-2.01 ± 6.33	1.22 (-8.97 – 15.37)
IC	**L**	1.63 (0.76 – 2.55)	1.86 (1.28 – 2.77)	-0.23 (-0.58 – 0.09)	-0.03 (-0.25 – 0.09)	-0.04 (-0.35 – 0.06)	0.03 (-0.48 – 0.48)
	% pred	71 (38 – 80)	77 (39 – 113)	-9.30 (-17.39 – 7.57)	-1.34 (-10.79 – 2.66)	-2.78 (-13.60 – 0.67)	0.16 (-11.88 – 21.08)
R_{aw}	**$kPa.s.L^{-1}$**	0.23 (0.17 – 0.36)	0.22 (0.11 – 0.36)	-0.02 (-0.09 – 0.08)	0.01 (-0.10 – 0.11)	0.01 (-0.05 – 0.13)	0.01 (-0.07 – 0.09)
sG_{aw}	**$L^2.kPa^{-1}.s^{-1}$**	1.68 (0.91 – 2.48)	1.76 (1.09 – 3.70)	0.09 (-0.78 – 0.84)	-0.18 (-1.33 – 0.92)	-0.09 (-1.04 – 0.10)	-0.12 (-1.95 – 0.60)
T_{LCO}	**$ml.min^{-1}.kPa^{-1}$**	2.7 (1.7 – 5.5)	4.0 (8.6 – 2.4)§	-0.2 (-1.3 – 0.4)	-0.2 (-0.9 – 1.5)	**-0.1 (-1.2 – 0.4)**	**0.4 (-0.8 – 1.7)‡**
	% pred	37 (22 – 70)	48 (32 – 80)§	-1.25 (-19.53 – 4.68)	-3.14 (-10.22 – 21.84)	**-0.76 (-18.34 – 5.07)**	**4.12 (-6.79 – 24.44)‡**
Resting Gas Exchange							
P_aO_2	**kPa**	8.9 (8.0 – 11.6)	10.8 (7.0 – 12.1)§	-0.15 (-1.40 – 1.19)	0.24 (-0.97 – 1.26)	-0.86 (-2.46 – 1.54)	0.00 (-1.26 – 1.02)§
P_aCO_2	**kPa**	4.9 (3.7 – 5.5)	5.2 (4.0 – 5.8)	0.29 (-0.95 – 0.67)	-0.45 (-1.14 – 0.74)§	0.23 (-0.71 – 0.55)	0.00 (-1.40 – 0.97)
$P_{(A-a)}O_2$	**kPa**	4.8 (2.7 – 7.4)	3.9 (2.4 – 6.7)	0.72 (-0.52 – 3.94)	0.27 (-2.10 – 0.70)	**0.88 (0.42 – 2.49)**	**-0.11 (-2.18 – 1.92)‡**
E_{rs} / WOB_{elas}							
$E_{rs,CPAP}$	**$kPa.L^{-1}$**	1.65 (0.80 – 5.31)	1.47 (0.61 – 1.83)	-0.06 (-1.31 – 0.28)	-0.03 (-0.89 – 0.66)	0.09 (-2.36 – 1.12)	-0.14 (-0.54 – 1.00)
$WOB_{elas,CPAP}$	**$J.min^{-1}$**	5.31 (3.11 – 20.22)	4.68 (1.70 – 8.44)	-0.67 (-5.92 – 3.83)	-0.32 (-4.35 – 5.73)	-0.17 (-10.60 – 11.31)	-0.43 (-3.37 – 6.01)
	$J.L^{-1}$	0.35 (0.29 – 1.16)	0.40 (0.21 – 0.62)	-0.01 (-0.34 – 0.12)	-0.03 (-0.27 – 0.24)	-0.00 (-0.40 – 0.41)	-0.01 (-0.28 – 0.28)

* $p<0.005$, † $p<0.01$, ‡ $p<0.05$, § $p<0.1$

Table 3.2.13. Endurance exercise test results over 12 months grouped by survival. Values are median (range). Significance testing was performed using the Mann Whitney U test looking at differences between the groups who died and survived at each timepoint.

		Baseline		Change over 6 months		Change over 12 months	
		Died (n=7)	Survived (n=15)	Died (n=7)	Survived (n=15)	Died (n=6)	Survived (n=13)
Endurance cycle exercise test							
T_{lim}	min	7.0 (2.7 – 12.6)	7.7 (4.9 – 16.6)	-0.35 (-3.27 – 0.51)	1.86 (-6.38 – 9.56)	**-2.26 (-7.42 – 1.42)**	**0.95 (-5.79 – 9.54)**‡
Resting variables							
RR	min^{-1}	23.7 (18.5 – 37.8)	21.6 (13.4 – 34.5)	-0.25 (-4.13 – 3.75)	-0.25 (-14.00 – 7.50)	1.05 (-3.75 – 13.75)	-0.50 (-11.79 – 8.50)
V_T	L	0.48 (0.39 – 0.68)	0.55 (0.33 – 0.76)	-0.02 (-0.07 – 0.06)	-0.01 (-0.17 – 0.43)	0.05 (-0.04 – 0.15)	0.06 (-0.07 – 0.19)
V_E	$L.min^{-1}$	12.4 (10.0 – 15.5)	10.5 (7.8 – 16.6)	-0.68 (-3.44 – 2.96)	-0.55 (-8.75 – 4.59)	2.91 (-0.23 – 5.55)	0.36 (-7.16 – 4.65)§
Isotime variables							
VO_2	$L.min^{-1}$	0.71 (0.28 – 0.91)	0.86 (0.52 – 1.73)§	0.01 (-0.15 – 0.10)	-0.02 (-0.23 – 0.10)	-0.04 (-0.08 - 0.00)	-0.05 (-0.30 – 0.12)
HR	min^{-1}	115 (99 – 126)	130 (85 – 162)	-5 (-19 – 13)	-11 (-24 – 6)	0 (-8 – 18)	-10 (-27 – 20)
RR	min^{-1}	33.8 (17.3 – 56.6)	38.3 (25.0 – 53.6)	**2.1 (-2.0 – 8.0)**	**-2.0 (-17.1 – 10.6)**‡	**6.6 (3.5 – 11.1)**	**-7.0 (-21.5 – 17.8)***
V_T	L	1.10 (0.52 – 1.39)	1.18 (0.63 – 2.59)	-0.011 (-0.29 – 0.18)	-0.02 (-0.35 – 0.42)	0.01 (-0.18 – 0.14)	0.05 (-0.30 – 0.26)
V_E	$L.min^{-1}$	39.0 (23.5 – 56.2)	42.8 (25.8 – 77.4)	**1.7 (-2.2 – 7.1)**	**-2.7 (-20.5 – 7.5)**‡	**5.6 (1.6 – 16.1)**	**-5.4 (-22.2 – 14.0)**‡
R		1.19 (0.74 – 1.40)	1.31 (1.13 – 1.43)	0.02 (-0.51 – 0.44)	-0.02 (-0.41 – 0.18)	**0.16 (-0.12 – 0.63)**	**-0.06 (-0.22 – 0.30)**‡
$Borg_{dysp}$		**3.0 (0.5 – 6.0)**	**5.0 (3.5 – 9.5)**‡	**1.0 (-1.0 – 2.5)**	**-1.0 (-4.0 – 1.0)**†	**1.75 (-1.0 – 4.0)**	**-2.0 (-5.0 – 3.0)**‡
$Borg_{leg}$		**4.0 (1.5 – 7.0)**	**7.0 (3.0 – 9.5)**‡	0.0 (0.0 – 2.0)	-1.0 (-8.0 – 2.5)§	**2.25 (0.0 – 5.5)**	**-1.0 (-4.0 – 2.0)**†
V_E/VO_2		65.1 (40.3 – 90.0)	46.0 (39.1 – 70.3)	2.4 (-29.5 – 15.4)	-1.4 (-16.4 – 10.1)	**20.8 (4.6 – 47.3)**	**-4.0 (-19.2 – 17.2)***
V_E/VCO_2		**51.0 (37.6 – 64.4)**	**39.9 (32.0 – 52.5)**‡	3.2 (-7.2 – 4.6)	-1.0 (-6.1 – 7.6)	**8.6 (-9.2 – 15.9)**	**-1.6 (-9.6 – 4.2)**‡
$\Delta P_{tc}O_2$,	kPa	-0.67 (-4.27 – 0.53)	-0.80 (-3.33 – 1.47)	-0.13 (-2.93 – 1.20)	-0.13 (-2.40 – 1.6)	**-1.20 (-1.60 – 0.80)**	**0.33 (-0.87 – 1.47)**‡
$P_{(A-tc)}O_2$	kPa	6.78 (4.76 – 10.71)	6.26 (1.72 – 8.90)	0.54 (-3.62 – 3.83)	-0.10 (-1.01 – 4.13)	**3.10 (0.71 -4.74)**	**-0.25 (-3.14 – 1.68)**†
V_D/V_T		0.60 (0.23 – 0.74)	0.40 (0.22 – 0.51)	0.02 (-0.08 – 0.08)	-0.06 (-0.25 – 0.32)	-0.03 (-0.17 – 0.25)	0.07 (-0.26 – 0.25)
$\Delta P_{tc}O_2/\Delta VO_2$	$kPa.min.L^{-1}$	-2.20 (-6.98 – 4.02)	-1.17 (-4.44 – 3.16)	-1.68 (-3.65 – 4.06)	-0.58 (-4.97 – 2.97)	-1.87 (-11.64 – 6.98)	0.20 (-1.75 – 5.04)

* $p<0.005$, † $p<0.01$, ‡ $p<0.05$, § $p<0.1$

Table 3.2.13 (Continued)

		Baseline		Change over 6 months		Change over 12 months	
		Died (n=7)	Survived (n=15)	Died (n=7)	Survived (n=15)	Died (n=6)	Survived (n=13)
End-exercise variables							
VO_{2peak}	$L.min^{-1}$	0.85 (0.43 – 1.10)	0.91 (0.58 – 1.77)	-0.03 (-0.22 – 0.29)	0.01 (-0.25 – 0.11)	-0.15 (-0.23 - -0.03)	0.03 (-0.36 – 0.62)[§]
HR	min^{-1}	116 (103 – 136)	132 (85 – 162)	1 (-13 – 13)	-4 (-33 – 8)	5 (-10 – 41)	-4 (-30 – 26)
RR	min^{-1}	42.1 (35.5 – 63.6)	37.4 (25.4 – 45.3)	1.1 (-2.6 – 9.0)	-0.3 (-6.5 – 11.1)	6.5 (-3.5 – 10.5)	-1.5 (-18.1 – 14.0)[§]
V_T	L	1.08 (0.56 – 1.26)	1.17 (0.56 – 2.61)	0.07 (-0.23 – 0.18)	-0.01 (-0.19 – 0.19)	-0.01 (-0.13 – 0.16)	0.02 (-0.34 – 0.58)
V_E	$L.min^{-1}$	45.2 (34.1 – 56.5)	47.1 (23.2 – 83.6)	5.0 (-7.5 – 7.3)	-0.6 (-8.0 – 16.3)	6.5 (-7.5 – 14.9)	-0.6 (-10.7 – 15.2)
R		1.28 (0.75 – 1.75)	1.28 (1.04 – 1.42)	0.03 (-0.71 – 0.41)	-0.00 (-0.35 – 0.21)	0.12 (-0.14 – 0.71)	0.03 (-0.20 – 0.26)
$Borg_{dysp}$		7.0 (4.0 – 10.0)	7.0 (4.0 – 10.0)	0.0 (-2.0 – 2.0)	-1.0 (-8.0 – 2.0)	-1.0 (-4.0 – 0.0)	0.0 (-4.0 – 2.0)
$Borg_{leg}$		9.0 (3.0 – 10.0)	9.0 (5.0 – 10.0)	0.0 (-3.0 – 4.0)	0.0 (-6.0 – 2.0)	0.5 (-5.0 – 4.0)	0.0 (-4.0 – 2.0)
V_E/VO_2		66.1 (45.8 – 107.1)	49.1 (33.3 – 68.7)	7.6 (-44.8 – 9.6)	-0.4 (-12.7 – 14.2)	**17.5 (8.5 – 46.7)**	**-1.4 (-22.8 – 13.4)**[*]
V_E/VCO_2		**51.5 (39.9 – 77.4)**	**41.5 (31.8 – 53.5)**[†]	-0.1 (-14.8 – 5.3)	0.9 (-5.3 – 4.8)	**10.8 (-11.5 – 15.9)**	**1.2 (-11.6 – 3.5)**[‡]
$\Delta P_{tc}O_2$,	kPa	-1.20 (-4.40 - -0.27)	-1.13 (-3.73 – 1.47)	-0.33 (-2.53 – 1.33)	-0.40 (-2.40 – 1.87)	-0.40 (-1.47 – 1.73)	0.27 (-1.07 – 2.00)
$P_{(A-tc)}O_2$	kPa	7.13 (4.80 – 11.29)	6.38 (1.75 – 9.34)	0.06 (-2.71 – 3.67)	0.23 (-1.45 – 4.73)	3.14 (-0.82 – 4.56)	-0.48 (-2.60 – 1.93)[§]
V_D/V_T		0.58 (0.24 – 0.71)	0.41 (0.18 – 0.54)	0.02 (-0.07 – 0.14)	-0.07 (-0.31 – 0.31)	0.02 (-0.21 – 0.39)	0.00 (-0.22 -0.23)
$\Delta P_{tc}O_2/\Delta VO_2$	$kPa.min.L^{-1}$	-1.84 (-6.80 - -0.35)	-1.58 (-5.26 – 2.94)	-1.22 (-3.39 – 4.39)	-0.50 (-4.51 – 3.91)	-1.58 (-6.82 – 6.80)	0.65 (-1.69 – 3.73)

[*] $p<0.005$, [†] $p<0.01$, [‡] $p<0.05$, [§] $p<0.1$

Table 3.2.14. Dyspnoea scale and HRQOL results over 12 months grouped by survival. Values are median (range). Significance testing was performed using the Mann Whitney U test looking at differences between the groups who died and survived at each timepoint.

	Baseline		Change over 6 months		Change over 12 months	
	Died (n=8)	Survived (n=15)	Died (n=8)	Survived (n=15)	Died (n=7)	Survived (n=14)
Dyspnoea scales						
MRC	3.5 (1.0 – 4.0)	3.0 (1.0 – 4.0)	0.0 (0.0 – 1.0)	0.0 (-1.0 – 1.0)	**1.0 (0.0 – 2.0)**	**0.0 (-1.0 – 1.0)**‡
CRP	10.0 (0.0 – 16.0)	6.0 (0.0 – 16.0)	1.0 (-2.0 – 4.0)	0.0 (-6.0 – 6.0)	**2.0 (0.0 – 6.0)**	**0.0 (-10.0 – 6.0)**‡
OCD	0.43 (0.26 – 1.0)	0.60 (0.33 – 1.0)	0.00 (-0.17 – 0.00)	0.00 (-0.31 – 0.18)	-0.10 (-0.19 – 0.16)	0.00 (-0.51 – 0.17)
BDI	3.5 (0.0 – 12.0)	6.0 (2.0 – 12.0)	-1.0 (-2.0 – 2.0)	0.0 (-3.0 – 5.0)	-1.0 (-4.0 – 2.0)	0.0 (-3.0 – 4.0)
SGRQ						
Symptoms	78.0 (23.6 – 97.5)	47.8 (7.5 – 92.8)	0.0 (-23.5 – 15.7)	-5.4 (-68.1 – 15.8)	**-4.1 (-14.9 – 53.5)**	**-14.5 (-51.5 – 14.7)**‡
Activities	79.4 (12.2 – 93.4)	73.0 (23.4 – 93.9)	-3.7 (-13.6 – 14.3)	0.0 (-24.6 – 18.1)	**0.0 (-0.1 – 20.2)**	**-9.0 (-24.6 – 6.0)**‡
Impacts	41.1 (1.9 – 66.2)	40.3 (1.6 – 64.6)	-5.3 (-24.0 – 4.5)	-1.6 (-20.4 – 20.7)	**4.6 (-20.1 – 29.7)**	**-15.1 (-32.3 – 22.0)**‡
Total	57.6 (9.2 – 79.6)	51.5 (14.4 – 75.5)	-1.1 (-18.1 – 8.8)	-1.8 (-21.6 – 14.1)	**5.0 (-11.4 – 30.0)**	**-14.9 (-23.3 – 12.8)**†
SF-36						
Physical functioning	25 (0 – 90)	40 (5 – 90)	-5 (-15 – 20)	-5 (-25 – 25)	-5 (-45 – 5)	5 (-25 – 20)§
Physical role	0 (0 – 100)	0 (0 – 100)	0 (-25 – 50)	0 (-50 – 75)	0 (-25 – 25)	0 (-75 – 100)
Bodily pain	89 (22-100)	67 (33-100)	0 (-11 – 44)	0 (-33 – 22)	0 (-33 – 22)	0 (-22 – 44)
General health	38 (10-72)	45 (10 – 87)	-5 (-25 – 30)	2 (-10 – 17)	**-5 (-27 – 10)**	**11.5 (-15 – 30)**‡
Vitality	45 (20 – 80)	40 (0 – 80)	**-5 (-35 – 5)**	**10 (-15 – 35)**‡	**-10 (-20 – 15)**	**10 (-10 – 40)**‡
Social functioning	72 (11 – 100)	67 (22 – 100)	0 (-22 – 56)	0 (-33 – 44)	-22 (-44 – 44)	0 (-22 – 22)
Emotional role	17 (0 – 100)	33 (0 – 100)	0 (-33 – 67)	0 (0 – 100)	0 (-100 – 67)	17 (-100 – 100)
Mental health	74 (52 – 92)	60 (48 – 96)	2 (-12 – 8)	0 (-36 – 28)	**-4 (-20 – 4)**	**4 (-12 – 20)**‡
Summary scores						
PCS	24.1 (7.3 – 50.3)	30.6 (14.3 – 53.2)	0.6 (-9.5 – 11.5)	0.0 (-11.3 – 12.0)	0.6 (-26.7 – 6.5)	3.7 (-10.2 – 13.5)
MCS	48.2 (35.6 – 59.7)	39.0 (29.7 – 62.8)	**-1.6 (-4.9 – 4.6)**	**2.6 (-2.1 – 18.8)**‡	**-3.2 (24.5 – 13.5)**	**2.2 (-7.6 – 19.9)**‡

* $p<0.005$, † $p<0.01$, ‡ $p<0.05$, § $p<0.1$

Figure 3.2.4. Change over 12 months in physiological variables, symptoms and HRQOL in the patients categorised by survival status (a) T_{LCO} (b) VC (c) $V_E/VO_{2,end}$ (d) $V_E/VO_{2,iso}$ (e) $P_{(A-tc)}O_{2,iso}$ (f) SGRQ Total Score

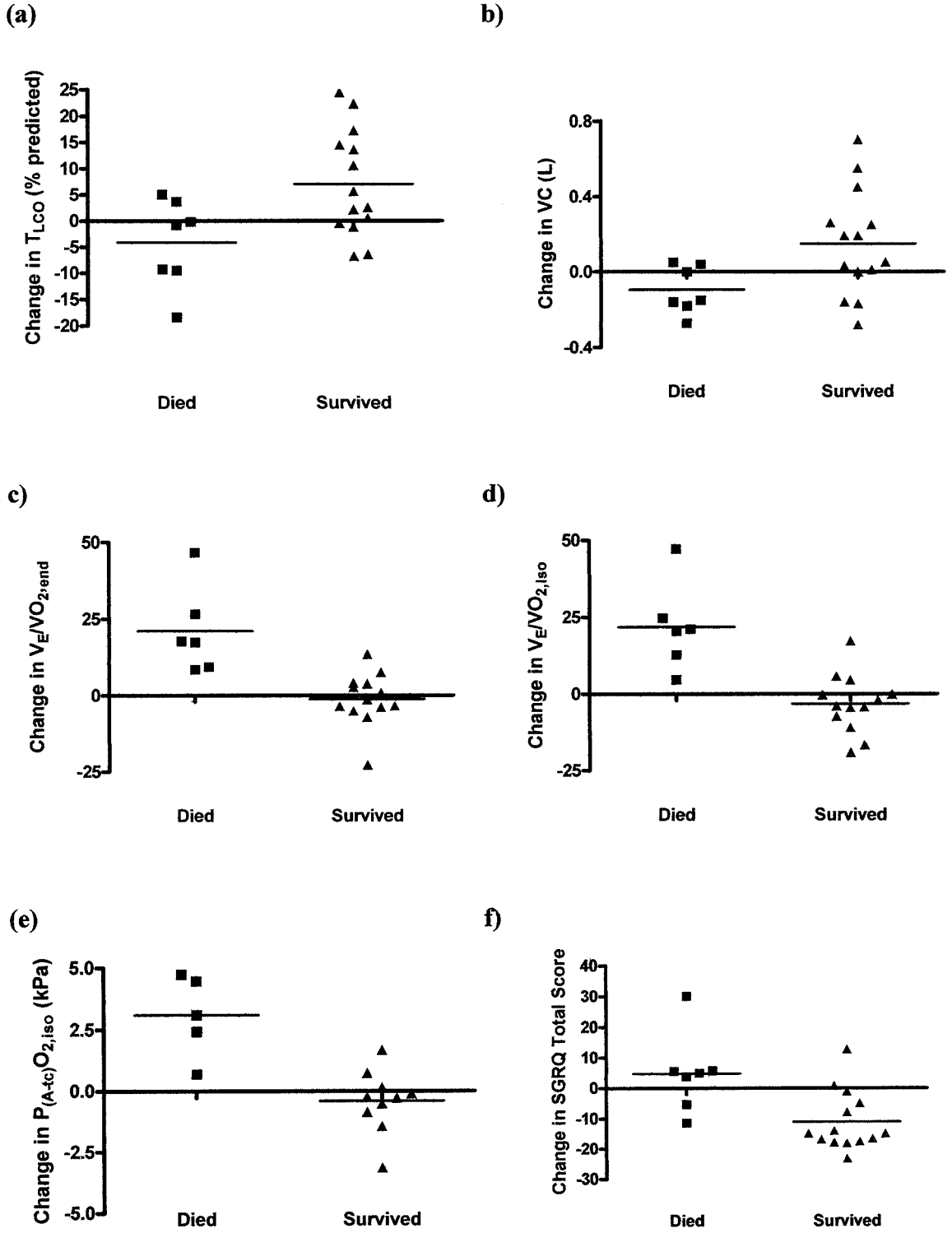


Table 3.2.15. Area under ROC curves for survival.

Variable		AUC
VC	abs	0.755
	% pred	0.852
T_{LCO}	abs	0.765
	% pred	0.821
FEV_1/VC	abs	0.776
	% pred	0.791
$P_{(A-a)}O_2$		0.872
T_{lim}		0.776
RR_{iso}		0.924
$V_{E,iso}$		0.814
$V_E/VO_{2,iso}$		0.929
$Borg_{dysp,iso}$		0.840
$Borg_{leg,iso}$		0.872
$\Delta P_{tc}O_2$		0.840
$P_{(A-tc)}O_{2,iso}$		0.970
$V_E/VO_{2,end}$		0.987
CRP		0.770
MRC		0.770
SGRQ (Total score)		0.878
SF-36 MCS		0.806
$E_{rs,CPAP}$		0.619
$WOB_{elas,CPAP}$ ($J.L^{-1}$)		0.519
$WOB_{elas,CPAP}$ ($J.min^{-1}$)		0.514

Figure 3.2.5. ROC curves showing relative performance of variables for predicting survival.

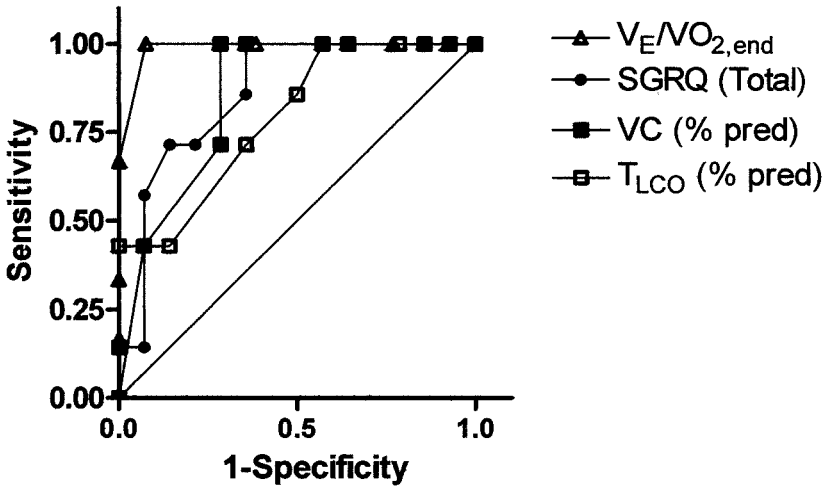
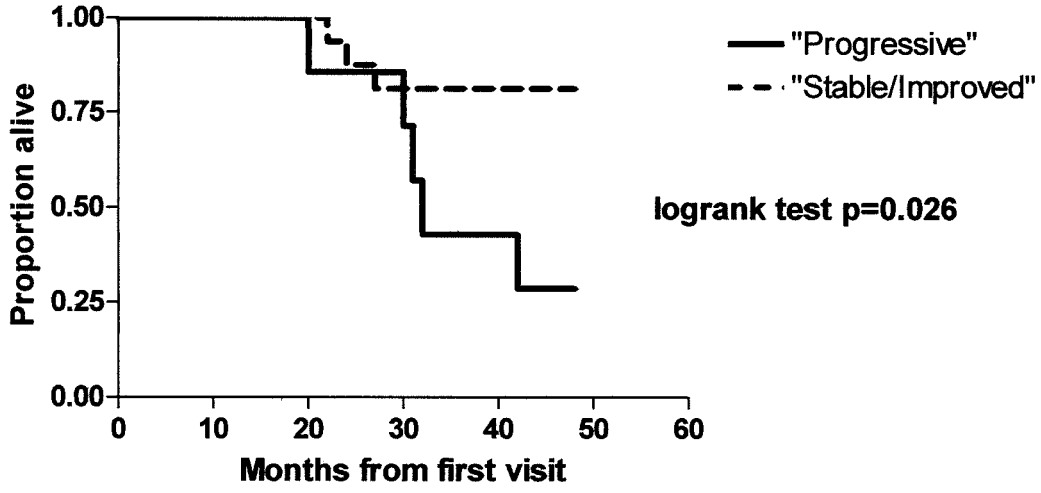


Table 3.2.16. Univariate analysis of survival using Cox proportional hazards regression. Twelve month changes in each variable were used (apart from age and smoking history).

Variable		Hazard Ratio	95% Confidence Intervals Lower	Upper	p-value
Age		1.113	0.982	1.262	0.09
Smoking status		1.011	0.241	4.237	0.99
VC	abs	**0.009**	**0.000**	**0.836**	**0.04**
	% pred	**0.775**	**0.637**	**0.942**	**0.01**
T_{LCO}	abs	**0.243**	**0.068**	**0.864**	**0.03**
	% pred	**0.871**	**0.777**	**0.977**	**0.02**
FEV_1/VC	abs	**1.164**	**1.020**	**1.328**	**0.02**
	% pred	**1.123**	**1.021**	**1.236**	**0.02**
$P_{(A-a)}O_2$		**2.380**	**1.126**	**5.029**	**0.02**
T_{lim}		0.813	0.646	1.022	0.08
RR_{iso}		**1.112**	**1.021**	**1.212**	**0.01**
$V_{E,iso}$		1.086	0.994	1.187	0.07
$V_E/VO_{2,iso}$		**1.132**	**1.041**	**1.232**	**0.004**
$V_E/VCO_{2,iso}$		**1.138**	**1.021**	**1.269**	**0.03**
$Borg_{dysp,iso}$		**1.434**	**1.000**	**2.057**	**0.05**
$Borg_{leg,iso}$		**2.748**	**1.259**	**5.998**	**0.01**
$\Delta P_{tc}O_2$		0.358	0.118	1.089	0.07
$P_{(A-a)}O_{2,iso}$		**1.789**	**1.152**	**2.779**	**0.01**
$V_E/VO_{2,end}$		**1.191**	**1.058**	**1.340**	**0.004**
$V_E/VCO_{2,end}$		**1.180**	**1.037**	**1.342**	**0.01**
CRP		1.292	0.979	1.704	0.07
MRC		**6.064**	**1.579**	**23.291**	**0.009**
SGRQ					
	Symptoms	**1.065**	**1.015**	**1.117**	**0.01**
	Activities	**1.181**	**1.048**	**1.330**	**0.006**
	Impacts	**1.061**	**1.009**	**1.116**	**0.02**
	Total	**1.109**	**1.033**	**1.190**	**0.004**
SF-36					
	General Health	**0.920**	**0.860**	**0.983**	**0.02**
	Vitality	**0.921**	**0.856**	**0.992**	**0.03**
	Mental Health	**0.902**	**0.825**	**0.986**	**0.01**
	MCS	**0.912**	**0.840**	**0.990**	**0.03**

Figure 3.2.6. Kaplan-Meier analysis grouping the subjects into those with "progressive" or "stable/improved" disease.
The significance of the difference between the two groups was assessed using the logrank test.



Discussion

In subjects with ILD, T_{LCO} and VC have the strongest evidence base as predictors of disease progression[2,324,327,328,330-333,338,341-343], this having been demonstrated both with baseline values and longitudinal changes over 6 months to 1 year. However, these variables may not capture all instances of disease worsening as it is possible to see deterioration in a subject without significant changes in VC and T_{LCO}[321]. In a study of interferon-γ1b in IPF, 44 patients died, with no definite change seen in VC or T_{LCO} in 19 (43%)[2].

In the original study design, it was not planned to compare changes in the measured variables with survival because it was thought that study numbers would be too small and study duration too short for this variable to be useful here. Instead a progression score was proposed as a surrogate marker of disease progression. This score was devised for the purposes of this study and has not had external validation against survival elsewhere. The variables included in the score were:-

- VC and T_{LCO}
- T_{lim} which has not previously been studied in this context
- dyspnoea, longitudinal changes being associated with survival in IPF[338]

- HRQOL which is significantly impaired in IPF[359].

The Kaplan-Meier analysis shown in Figure 3.2.6 illustrates that the progression score did predict survival. The variables able to predict poor prognosis as indicated by this progression score are shown in Tables 3.2.8 to 3.2.10. Variables from resting pulmonary function, endurance exercise tests and dyspnoea and HRQOL scores were all useful in this regard. $E_{rs,CPAP}$ and $WOB_{elas,CPAP}$ appeared to perform particularly well.

With the availability of survival data, this analysis was repeated using this more objective endpoint and the relevant data are shown in Tables 3.2.12 to 3.2.14. It can be seen that there were only a small number of significant differences at baseline between the group who died in the follow-up period and those who survived. The former had a more restrictive pattern on pulmonary function tests (reduced VC, FEV_1 and TLC), increased ventilatory inefficiency during exercise (increased V_E/VCO_2) but there was no baseline difference in symptoms or HRQOL. At six months, the changes in each group did not differ in terms of lung volumes and gas transfer but on endurance exercise testing the group who died showed an increase in $V_{E,iso}$ (due to increased RR) and $Borg_{dysp,iso}$, suggesting greater ventilatory requirements for the same workload. By twelve months the two groups had begun to diverge more widely. At this assessment, the group who died during follow-up showed the typical pattern of worsening ILD, namely significantly lower VC and T_{LCO} and greater FEV_1/VC and $P_{(A-a)}O_2$. On exercise testing, they showed a fall in T_{lim} and widespread differences in performance at isotime. This included increases in RR, V_E, R, V_E/VO_2, V_E/VCO_2, Borg scores, $P_{(A-tc)}O_2$ and a greater fall in $P_{tc}O_2$. Differences at end-exercise were less widespread, isolated to a greater increase in ventilatory equivalents. Differences in changes in symptoms and HRQOL had also become apparent by twelve months. In particular the group who died showed significant relative increases in CRP, MRC and SGRQ scores. The changes in the latter exceeded the recognised minimum clinically important difference of 4 units. The promising performance of $E_{rs,CPAP}$ and $WOB_{elas,CPAP}$ seen in the progression score analysis was not replicated when looking at survival.

The ability of change in each variable to act as a predictive test of subsequent death or survival was assessed by AUC measurements from ROC curves (Table 3.2.15). An AUC of 0.5 indicates that the variable is no better predictor than chance and 1.0 suggests the variable is 100% sensitive and specific. End-exercise and isotime V_E/VO_2 proved to be the most discriminating tests. Other variables which performed particularly well (i.e. AUC > 0.9) were

isotime RR and $P_{(A-tc)}O_2$. Figure 3.2.5 illustrates the relative performance of $V_E/VO_{2,end}$, SGRQ Total score, VC and T_{LCO}. Cox proportional hazards regression was then used to corroborate the ROC curve findings and a similar distribution of variables were found to be significant on univariate analysis.

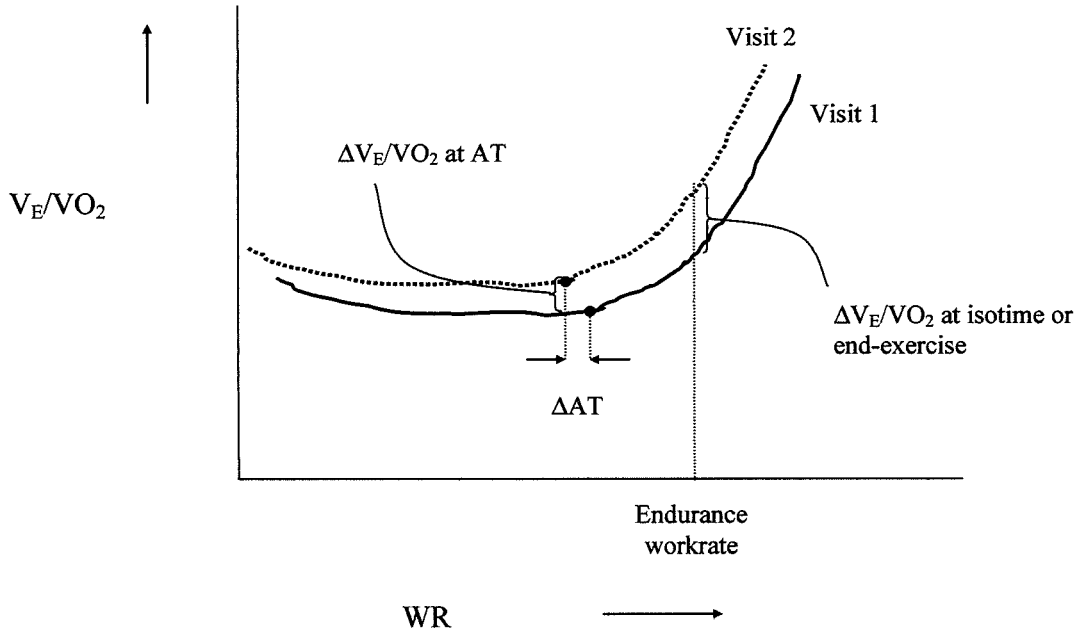
The results of this study suggest that longitudinal changes in endurance exercise test variables and HRQOL appear to be potentially more successful than conventional variables such as VC and T_{LCO} at predicting survival in ILD. Two particularly encouraging strategies which emerged from the exercise testing were the use of V_E/VO_2 at both isotime and end-exercise and use of the isotime variables in general. Assessing the patients at isotime effectively meant that they had been exposed to the same workload for the same duration on each occasion. By this stage in the exercise test, the variables measured (RR, V_E, VO_2, VCO_2) were principally dictated by the subject's physiology rather than any volitional factors which was not true of end-exercise variables nor of the results of maximal voluntary manoeuvres such as FEV_1 and FVC. As a consequence, this rendered measurement of isotime variables relatively objective compared with other measurements.

The particular success of end-exercise and isotime V_E/VO_2 was surprising but perhaps can be explained by the exponential nature of the relationship of V_E/VO_2 with WR demonstrated above the AT in an incremental cardiopulmonary exercise test. This is shown schematically in Figure 3.2.7. Patients who deteriorate will in general demonstrate greater ventilatory equivalents throughout the test in combination with a lower AT. This effect is demonstrated as a dashed line in Figure 3.2.7. The work rate of the endurance exercise test at 70% of maximum work rate during an incremental test would typically be above the AT. If the subject deteriorates between visits, a small change in AT and V_E/VO_2 at AT will be amplified by the shape of the curve into a large change in V_E/VO_2 towards the end of an endurance exercise test.

A limitation of this study was the small number of subjects, representing the consenting cohort of patients with ILD attending the respiratory outpatient clinics at GRI and, probably because of this, multivariate Cox proportional hazards regression did not prove helpful. The findings in this study therefore need to be reproduced in a larger cohort. The study population was also heterogeneous, approximately half having IPF, the others having ILD of mixed aetiology. Although there are broad similarities in physiology across subjects with ILD, there

are also discernible differences[347] which could weaken the study conclusions. This criticism is also a strength as this study is generalisable to the subject population attending an ILD clinic rather than simply subjects with IPF.

Figure 3.2.7. Schematic depiction of the relationship between V_E/VO_2 and WR during an incremental cardiopulmonary exercise test for a subject with ILD who deteriorates between visit 1 and visit 2.
The endurance workrate is the same at each visit and the consequent change in V_E/VO_2 ($\Delta V_E/VO_2$) is amplified during the endurance test compared with the change seen at AT (ΔAT).



Conclusions

- For unselected subjects with ILD, endurance exercise tests and the SGRQ questionnaire proved superior longitudinal outcome measures for predicting survival relative to the conventional tests in the group of subjects studied. Variables measured at isotime during the endurance exercise test proved to be particularly discriminating, the most successful being V_E/VO_2.
- Longitudinal changes in $E_{rs,CPAP}$ and $WOB_{elas,CPAP}$ appeared to perform well at predicting progression scores but this was not translated into an ability to predict survival in this cohort.

3.3 Measuring recovery from exacerbation of chronic obstructive pulmonary disease

Introduction

COPD is a disorder characterised by both long-term symptoms and acute exacerbations. The importance of exacerbations in determining disease progression has recently been highlighted. Patients with frequent exacerbations show poorer HRQOL[386] and possibly faster rate of decline of HRQOL[387,388]. There is also evidence to suggest that frequent exacerbations lead to faster physiological decline measured by both FEV_1 and PEF[389,390]. It has been known for some time that functional ability measured by activities of daily living may be permanently impaired in elderly patients with COPD[391]. In this study at three months after discharge, approximately 30% of patients had not regained their previous mobility and 65% were unable to do housework that they could previously manage.

Changes in lung function, symptoms and HRQOL have previously been evaluated within exacerbations. Change in lung function has been demonstrated both by PEF[392-395] and spirometry[394,396,397]. The largest rates of change occurred in the first few days of the exacerbation and larger increases in FEV_1 over the first two days were predictive of superior clinical outcome[398]. Recovery was sometimes slow or incomplete with only 75% regaining their original PEF by 35 days after the exacerbation and 7.1% not returning to baseline lung function at 3 months[394]. Changes in symptoms have been determined using patient diaries[392,394,399], with the onset of symptoms occurring before changes in lung function[394]. Improvement in disease specific HRQOL following a transient fall due to an exacerbation has been demonstrated using the St George's Respiratory Questionnaire (SGRQ)[400] and the Chronic Respiratory Disease Questionnaire (CRQ)[395,401], with a review of the subject recently published by Doll[402]. Improvement in HRQOL following an exacerbation has been shown to be curtailed if a further exacerbation occurs close on the first[387].

The use of forced oscillometry has several potential advantages in assessing the physiological status of patients with an exacerbation of COPD. Firstly, it is a passive manoeuvre which requires only tidal breathing and therefore is easy to perform by breathless patients in

respiratory failure. Secondly, within-breath measurements of X_{rs} could be used to quantify simultaneously both airway resistance and degree of expiratory flow limitation. By contrast, R_{rs} is less likely to be helpful in subjects with significant irreversible airways obstruction such as in COPD because of the phenomenon of upper airway wall shunt which degrades the relationship between R_{rs} and airway resistance in this situation. To date only one study has reported forced oscillometry data during an exacerbation of COPD[403]. They confirmed the expectation that R_{rs} would not change but that X_{rs} would rise significantly towards more normal values as the exacerbation resolved. Within breath X_{rs} data during an exacerbation of COPD have not been reported.

Aim

The aim of this study was to assess the ability of forced oscillometry and measurements derived from it (work of breathing and % flow limitation) to detect longitudinal physiological changes during an exacerbation of COPD by comparison with spirometry, gas exchange, symptoms and HRQOL.

Methods

Subjects

Patients with a clinical diagnosis of COPD admitted to the medical receiving ward or referred to the Acute Respiratory Assessment Service at GRI were approached to take part in the study. They were within 48 hours of the point of presentation when first assessed, age > 40 years, smoking history > 20 pack years and had baseline spirometry which satisfied the British Thoracic Society definition of COPD (i.e. FEV_1 < 80% predicted and FEV_1/FVC ratio < 70%)[223]. They had recognised features of an exacerbation, the criteria used here being increased breathlessness for at least 24 hours with at least two of increased cough frequency or severity, increased sputum volume or purulence or increased wheeze[214]. The only exclusion criterion was decompensated respiratory failure. A smaller group of asthmatic subjects were also enrolled for comparison. It was anticipated that the asthmatics would have

much larger physiological changes than the COPD subjects which would highlight problems with the experimental method if they could not be detected.

Study Design

This was a longitudinal observational study (design summarised in Figure 3.3.1). At the start of each visit the subject received 5 mg of nebulised salbutamol and measurements were performed after 20 minutes. The drug was delivered over 10 to 15 minutes in a 2.5 ml volume using a jet nebulizer (Micro-Neb Nebuliser, Lifecare Hospital Supplies) driven by an airflow of 8 $L.min^{-1}$ (Aquilon Nebuliser System, AFP Medical) through a face mask (Duo Mask Adult, Lifecare Hospital Supplies). Visit 2 was scheduled to occur at approximately one week following visit 1 and visit 3 at 6 weeks. If the patient suffered a relapse between visits 2 and 3 which required hospital admission or further treatment by the Hospital at Home team, visit 3 was postponed until the patient was in a stable condition at home and on normal treatment. One operator (MKJ) performed all tests and was blinded to the results of earlier tests.

Figure 3.3.1. Study protocol showing order of tests.

Visit 1 (<48 hours)
Visit 2 (1 week)
Visit 3 (6 weeks)

- Demographic data (visit 1 only)
- Symptom scores
- Dyspnoea scales
- Activities of daily living
- HRQOL (visits 1 & 3 only)
- Forced oscillometry, RWV, PTT, E_{rs}
- Capillary blood gases
- Spirometry

All conventional techniques were described in detail in Chapter 1.3. Symptoms were assessed using visual analogue scales derived from Davies[214] and a simple numerical scale used by Paggiaro[215]. Dyspnoea was measured by four scales, visual analogue scale, modified Borg score[199], OCD[210] and the BDI/TDI[211]. Activities of daily living were assessed using the LCADL Questionnaire[208]. HRQOL was assessed using the SGRQ[200]. Pulmonary function was assessed using spirometry, and capillary earlobe blood gases. All the tests described in

Chapter 1.2 were performed and analysed (including E_{rs} and WOB_{elas}). Only oscillometry, RWV and PTT results were shown as these were the relevant variables in an obstructive setting. Not surprisingly E_{rs} and WOB_{elas} showed little change.

Sample Size

The power calculation for this section was the same as for the study in Chapter 3.1. To detect a change in R_{rs} of ~0.05 kPa.s.L^{-1} with a standard deviation for the change of ~0.15 kPa.s.L^{-1} with 80% power and a significance level of 0.05, the sample size required was 35[310,311]. Given that some attrition was expected because of the frail condition of the study subjects, it was decided to aim for 50 patients in total.

Statistical Analysis

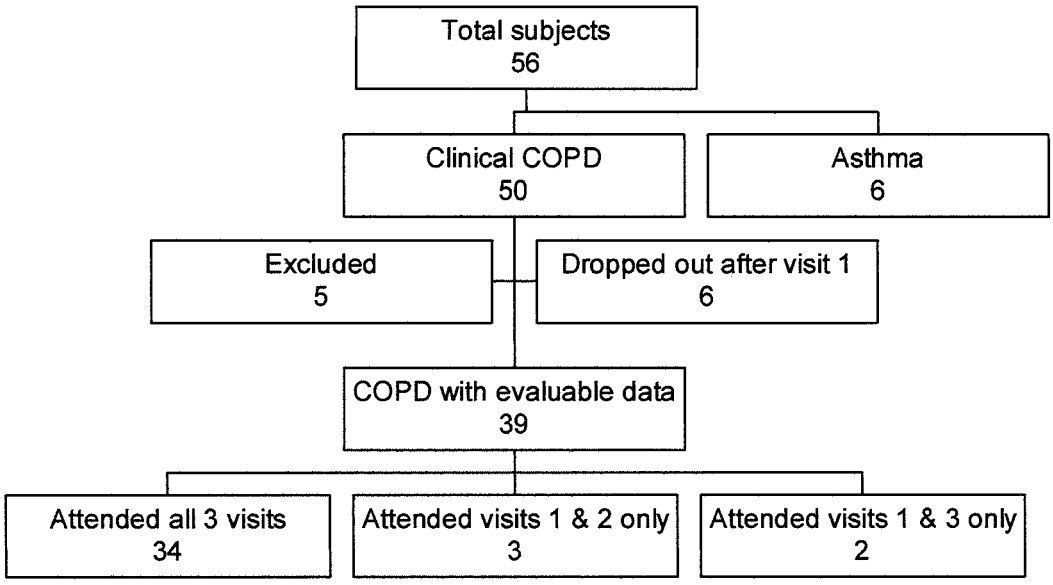
Baseline results were summarised either as mean (SD) or median (range) and changes as mean ± SEM. The changes in each test parameter were analysed between visit 2 and visit 1, visit 3 and visit 1 and visit 3 and visit 2 using the Student paired t test for COPD subjects (normally distributed data) and Wilcoxon signed rank test for asthmatics. The level of statistical significance was taken as 0.05. No compensation for multiple comparisons (such as the Bonferroni method) was explicitly applied and this should be taken into consideration when interpreting the significance of results. To compare the relative utility of each variable, a sensitivity index[4] was calculated from the size of the change divided by the coefficient of variation obtained from Chapter 3.1. To assess the relationship between changes in physiological variables and symptoms or HRQOL, Pearson correlation coefficients were calculated for changes in the key variables between visit 1 and visit 3. All statistics where performed with Statview v 5.0.1 (SAS Institute Inc.) or SPSS v 12.0.1 (SPSS Inc.).

Results

Subjects

The recruitment of subjects into this study is summarised in Figure 3.3.2. Of 50 COPD subjects who initially consented to the study, 5 were excluded (3 by spirometry showing absence of airways obstruction at least once during the visits and 2 were non-smokers with bronchiectasis). A further 6 failed to attend after the first visit leaving evaluable data on 39 subjects. The COPD subjects successfully completed all the study protocol at the visits they attended and all had airways obstruction at their final visit after recovery from the exacerbation. Of the asthmatics, attendance was complete except for 2 who missed visit 2.

Figure 3.3.2. Flowchart showing subject recruitment.



Baseline Results

The data in Table 3.3.1 summarise the physiological status of the subjects at visit 1 of their exacerbation. Mean spirometry values showed moderate airways obstruction with a reduced IC similar to the values given by Parker[395]. Approximately half the subjects were in respiratory failure (mainly Type 1). The oscillometry results showed increased magnitude of R_{rs} and X_{rs} components and the derived variables ($WOB_{FOT,Xinsp}$ and % flow limitation) compared with stable COPD (see Chapter 3.1). The patients were more symptomatic than normal reflected by their VAS scores for sleep, wheeze and mobility and by their values on the TDI scale. Activities of daily living were severely impaired and HRQOL was poor, with SGRQ values generally higher than those quoted by Spencer[400].

Table 3.3.1. Baseline values from Visit 1.
All data are mean (SD) unless otherwise indicated.

			COPD	Asthma
Number			39	6
Sex (male : female)			16:23	3:3
Age (years)			63.1 (6.9)	47.0 (14.5)
Weight (kg)			61.8 (16.5)	90.7 (16.1)
Height (m)			1.59 (0.09)	1.64 (0.07)
BMI ($kg.m^{-2}$)			24.4 (6.3)	33.6 (5.4)
Smoking history				
- **ex or current smokers : lifelong non-smokers**			39:0	4:2
- **pack years**			40 (10-100)$^{+}$	20 (3-40)$^{+}$
Exacerbation frequency (yr^{-1})			3.9 (2.9)	3.0 (2.7)
Time interval (days)				
- **admission to visit 1**			2 (0 - 3)$^{+}$	2 (1 - 3)$^{+}$
- **visit 1 to visit 2**			7 (3 - 15)$^{+}$	12 (7 - 21)$^{+}$
- **visit 1 to visit 3**			42 (35 - 102)$^{+}$	42 (33 - 65)$^{+}$
Symptoms				
Increased dyspnoea (%)			100	100
Increased cough (%)			89	83
Increased sputum (%)			61	33
Increased wheeze (%)			61	100
Spirometry				
VC	**L**		2.45 (0.90)	2.90 (0.92)
	% pred		88 (25)	80 (13)
FEV_1	**L**		0.96 (0.42)	1.71 (0.74)
	% pred		43 (16)	56 (16)
FEV_1/VC	**%**		40 (10)	58 (14)
PEF	**$L.s^{-1}$**		2.75 (1.11)	4.16 (1.36)
	% pred		43 (16)	55 (15)
IC	**L**		1.70 (0.65)	2.52 (0.88)
	% pred		77 (28)	95 (23)
Capillary earlobe blood gases				
P_aO_2	**kPa**		8.07 (1.35)	8.28 (1.41)
P_aCO_2	**kPa**		4.74 (0.77)	4.98 (0.86)
Breathing pattern				
Respiratory rate		**min^{-1}**	19.3 (5.6)	16.6 (7.1)
Tidal volume		**L**	0.737 (0.249)	0.939 (0.771)

Table 3.3.1 (continued)

		COPD	Asthma
Oscillometry			
R_{rs}	$kPa.s.L^{-1}$	0.605 (0.194)	0.702 (0.310)
X_{rs}	$kPa.s.L^{-1}$	-0.594 (0.269)	-0.469 (0.351)
$R_{rs,insp}$	$kPa.s.L^{-1}$	0.517 (0.152)	0.632 (0.285)
$X_{rs,insp}$	$kPa.s.L^{-1}$	-0.298 (0.117)	-0.204 (0.087)
$R_{rs,exp}$	$kPa.s.L^{-1}$	0.658 (0.231)	0.743 (0.323)
$X_{rs,exp}$	$kPa.s.L^{-1}$	-0.776 (0.389)	-0.629 (0.494)
$WOB_{FOT,Xinsp}$	$J.min^{-1}$	10.6 (7.9)	4.72 (2.13)
	$J.L^{-1}$	0.762 (0.416)	0.423 (0.214)
%FL	%	50 (29)	35 (30)
Pulse transit time			
ΔPTT_{max} (ms)		12.3 (8.4)	9.0 (6.2)
ΔPTT_{ave} (ms)		6.7 (5.1)	3.2 (5.0)
Respiratory waveform variation			
RWV_{diff} (AU)		0.103 (0.068)	0.075 (0.034)
RWV_{area} (AU)		0.053 (0.036)	0.032 (0.016)
Symptom score			
VAS			
Sleep		-37.6 (42.7)	-32.5 (37.9)
Wheeze		-39.4 (36.0)	-30.8 (38.8)
Mobility		-65.8 (34.5)	-44.2 (42.4)
Paggiaro		9.18 (2.73)	8.83 (2.79)
Dyspnoea			
VAS		39.7 (25.9)	52.5 (29.3)
BDI		3.79 (2.58)	7.00 (3.79)
TDI		-5.41 (1.55)	-6.40 (1.95)
OCD		0.280 (0.088)	0.439 (0.299)
Borg		3.62 (1.54)	3.83 (2.40)
Impairment of activities of daily living (LCADL)		54.1 (5.8)	49.8 (7.95)
Health related quality of life (SGRQ)			
Symptoms		83.1 (13.9)	72.1 (16.3)
Activities		87.9 (11.9)	63.2 (27.3)
Impacts		62.8 (16.2)	45.1 (26.9)
Total		73.8 (12.5)	55.0 (24.3)

[+] Median (range)

Change during Exacerbation

The changes in physiological variables during the exacerbation are shown in Table 3.3.2. Percentage change values were derived in different ways for the spirometry and oscillometry variables. As lung volumes and flows were typically reduced and reliable predicted values available, these were given as % change relative to the predicted values. Since oscillometry values were higher than normal during the exacerbation and predicted values less well known, the denominator for % change was the average of the values at the relevant visit. These results are also summarised in Figure 3.3.3. The changes between visits 2 and 3 are not shown in detail as they were smaller and generally not significant (with the exception of FEV_1, PEF, $X_{rs,insp}$, Paggiaro symptom score, TDI, Dyspnoea (VAS) and LCADL which were marginally significant). This time course of change is illustrated in Figure 3.3.4.

To obtain a measure of the "signal to noise" content or sensitivity index of the physiological measurements[4], the changes between visits 1 and 3 are shown in Table 3.3.3 divided by the reproducibility or coefficient of variation of the measurement (Chapter 3.1). FEV_1, VC and IC were the more reliable measurements followed by the X_{rs} variables.

Table 3.3.2. Change in variables between visits for all patients. All data are mean ± SEM.
The statistical significance of paired changes was assessed using the Student paired t test for COPD subjects and Wilcoxon signed rank test for asthmatics. The statistical significance of % changes was assessed using the equivalent one sample test, with the null hypothesis being a mean change of zero.

			COPD		Asthma	
			Visit 2 – Visit 1 n=37	Visit 3 – Visit 1 n=36	Visit 2 – Visit 1 n=4	Visit 3 – Visit 1 n=6
Spirometry						
VC	**L**		**0.297 ± 0.061**§	**0.354 ± 0.071**§	0.320 ± 0.311	**0.782 ± 0.125**†
	% pred		**10.3 ± 1.8**§	**12.1 ± 2.3**§	5.24 ± 11.5	**21.1 ± 2.3**†
FEV_1	**L**		**0.153 ± 0.046**‡	**0.274 ± 0.064**§	0.535 ± 0.273	**0.823 ± 0.164**†
	% pred		**6.37 ± 1.71**‡	**11.4 ± 2.3**§	15.7 ± 9.8	**26.9 ± 4.1**†
FEV_1/VC	**%**		0.200 ± 1.100	3.18 ± 1.47 †	10.3 ± 1.1*	**9.98 ± 3.32** †
PEF	**$L.s^{-1}$**		**0.455 ± 0.140**‡	**0.696 ± 0.142**§	1.05 ± 0.58	**1.86 ± 0.37**†
	% pred		**6.80 ± 2.18**‡	**11.0 ± 2.2**§	13.1 ± 8.2	**24.3 ± 4.5**†
IC	**L**		**0.241 ± 0.054**§	**0.295 ± 0.056**§	0.259 ± 0.225	**0.478 ± 0.155**†
	% pred		**9.87 ± 1.98**§	**11.9 ± 2.3**§	8.97 ± 10.7	**17.8 ± 4.9**†
Capillary earlobe blood gases						
P_aO_2	**kPa**		**0.85 ± 0.18**§	**1.18 ± 0.21**§	1.95 ± 0.24*	**1.64 ± 0.45**†
P_aCO_2	**kPa**		0.06 ± 0.13	0.02 ± 0.14	-0.40 ± 0.36	-0.11 ± 0.30
Breathing pattern						
Respiratory rate		**min^{-1}**	**-1.37 ± 0.65**†	**-1.57 ± 0.64**†	0.53 ± 0.78	-2.22 ± 1.90
Tidal volume		**L**	-0.002 ± 0.029	0.008 ± 0.183	-0.402 ± 0.428	0.056 ± 0.144

* $p<0.1$, † $p<0.05$, ‡ $p<0.005$, § $p<0.0005$.

Table 3.3.2 (Continued).....

		COPD		Asthma	
		Visit 2 – Visit 1 n=37	**Visit 3 – Visit 1 n=36**	**Visit 2 – Visit 1 n=4**	**Visit 3 – Visit 1 n=6**
Oscillometry					
R_{rs}	**kPa.s.L^{-1}**	-0.025 ± 0.020	-0.009 ± 0.024	-0.185 ± 0.067*	**-0.105 ± 0.037†**
	%	-3.60 ± 3.47	-0.95 ± 3.9	-31.3 ± 9.9	-16.4 ± 7.2
X_{rs}	**kPa.s.L^{-1}**	**0.132 ± 0.034§**	**0.143 ± 0.039‡**	0.165 ± 0.066*	**0.298 ± 0.108†**
	%	**27.9 ± 7.0§**	**35.2 ± 8.9§**	45.2 ± 4.8	**82.3 ± 15.8†**
$R_{rs,insp}$	**kPa.s.L^{-1}**	-0.025 ± 0.015	-0.024 ± 0.019	-0.122 ± 0.078	**-0.093 ± 0.034†**
	%	-4.97 ± 3.25	-3.91 ± 3.90	-21.8 ± 13.4	-16.1 ± 8.0
$X_{rs,insp}$	**kPa.s.L^{-1}**	**0.032 ± 0.011†**	**0.073 ± 0.017§**	-0.012 ± 0.041	**0.072 ± 0.018†**
	%	**13.0 ± 4.5†**	**27.4 ± 6.7§**	9.19 ± 14.6	**47.6 ± 15.0†**
$R_{rs,exp}$	**kPa.s.L^{-1}**	-0.020 ± 0.027	0.006 ± 0.030	-0.219 ± 0.064*	-0.100 ± 0.040*
	%	-2.57 ± 4.09	1.25 ± 4.22	-35.7 ± 8.8	-14.8 ± 7.2
$X_{rs,exp}$	**kPa.s.L^{-1}**	**0.193 ± 0.050§**	**0.180 ± 0.054‡**	0.248 ± 0.103*	**0.431 ± 0.152†**
	%	**31.5 ± 7.8§**	**37.1 ± 10.0‡**	60.8 ± 8.9	**96.0 ± 14.2†**
%FL	**%**	**-14.8 ± 4.5‡**	**-16.9 ± 4.8‡**	-9.76 ± 10.54	**-32.5 ± 11.1†**
Pulse transit time					
ΔPTT_{max} (ms)		-0.16 ± 0.80	-0.98 ± 1.88*	0.91 ± 4.11	1.71 ± 2.59
ΔPTT_{ave} (ms)		-0.45 ± 0.51	**-2.31 ± 0.85†**	0.92 ± 3.85	0.93 ± 2.05
Respiratory waveform variation					
RWV (AU)		0.0028 ± 0.0069	**-0.0304 ± 0.0094‡**	-0.021 ± 0.014	-0.038 ± 0.016
RWV_{area} (AU)		0.0014 ± 0.0036	**-0.0174 ± 0.0046§**	-0.013 ± 0.009	-0.014 ± 0.008*

* $p<0.1$, † $p<0.05$, ‡ $p<0.005$, § $p<0.0005$.

Table 3.3.2 (Continued).....

	COPD		Asthma	
	Visit 2 – Visit 1 n=37	**Visit 3 – Visit 1 n=36**	**Visit 2 – Visit 1 n=4**	**Visit 3 – Visit 1 n=6**
Symptom score				
VAS				
Sleep	**30.5 ± 8.1**‡	**23.5 ± 9.3**†	30.0 ± 24.2	45.8 ± 18.7*
Wheeze	**17.7 ± 6.5**†	**22.6 ± 8.4**†	27.0 ± 18.8	27.5 ± 17.4
Mobility	**31.8 ± 6.5**§	**37.1 ± 7.6**§	50.0 ± 17.7*	**45.8 ± 18.8**†
Paggiaro	**-1.70 ± 0.54**‡	**-3.14 ± 0.62**§	**-4.60 ± 0.75**	**-5.80 ± 1.20**†
Dyspnoea				
VAS	**16.9 ± 4.3**§	**27.0 ± 5.7**§	**31.0 ± 9.27**	36.6 ± 14.6*
TDI	**1.92 ± 0.33**§	**3.39 ± 0.405**§	5.00 ± 2.12*	6.00 ± 1.87*
OCD	**0.068 ± 0.018**‡	**0.101 ± 0.027**‡	0.192 ± 0.126	0.318 ± 0.151
Borg	**-0.973 ± 0.205**§	**-1.15 ± 0.281**‡	-2.80 ± 1.20*	-2.92 ± 1.24*
Impairment of activities of daily living (LCADL)	**-7.24 ± 0.90**§	**-11.6 ± 1.3**§	-14.5 ± 7.2*	**-23.4 ± 5.2**†
SGRQ				
Symptoms		0.121 ± 2.41		-3.80 ± 3.86
Activities		**-4.76 ± 2.26**†		**-25.0 ± 10.5***
Impacts		**-9.88 ± 2.92**‡		**-22.4 ± 7.7**†
Total		**-6.67 ± 1.96**‡		**-20.1 ± 7.0**†

* $p<0.1$, † $p<0.05$, ‡ $p<0.005$, § $p<0.0005$.

Figure 3.3.3. Comparison of the magnitude of the percentage changes in spirometry and oscillometry parameters between visit 1 and visit 3 for the COPD subjects.
Spirometry values are given as change in % predicted. % changes in oscillometry parameters were calculated by averaging the results from the first and last visits and using this as the denominator. Error bars show SEM.

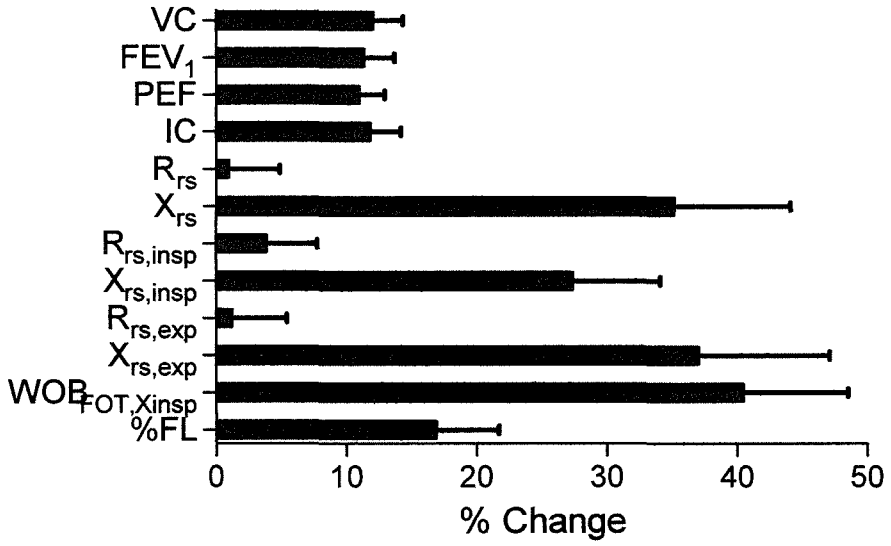
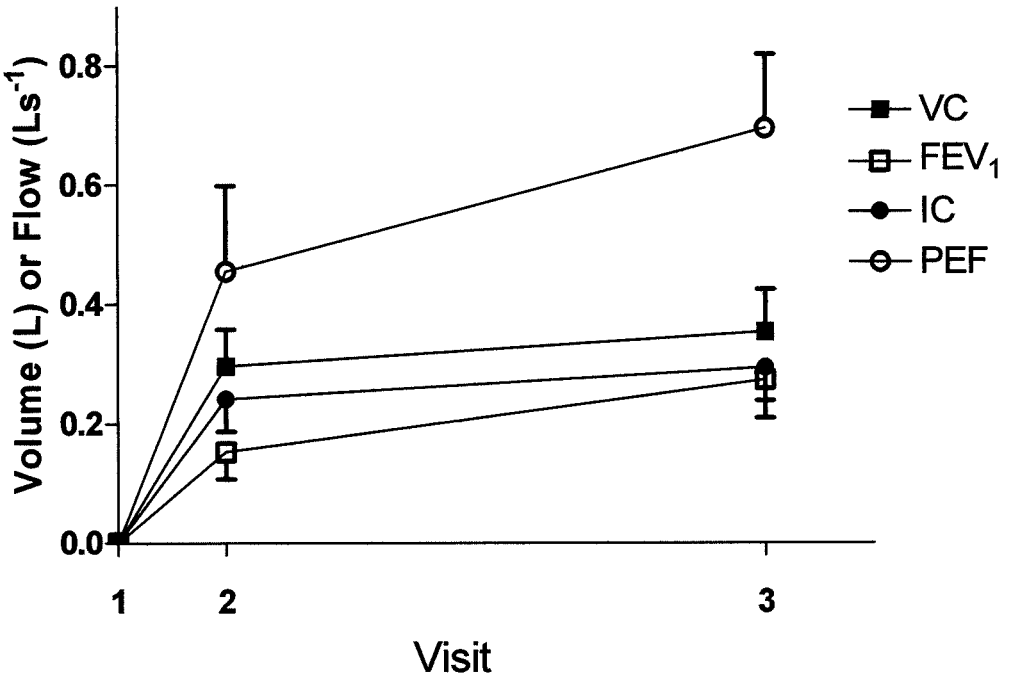


Table 3.3.3. Sensitivity index of spirometry and oscillometry measurements in COPD subjects.
This analysis uses % change rather than % predicted values for spirometry in order to be comparable with the coefficient of variation.

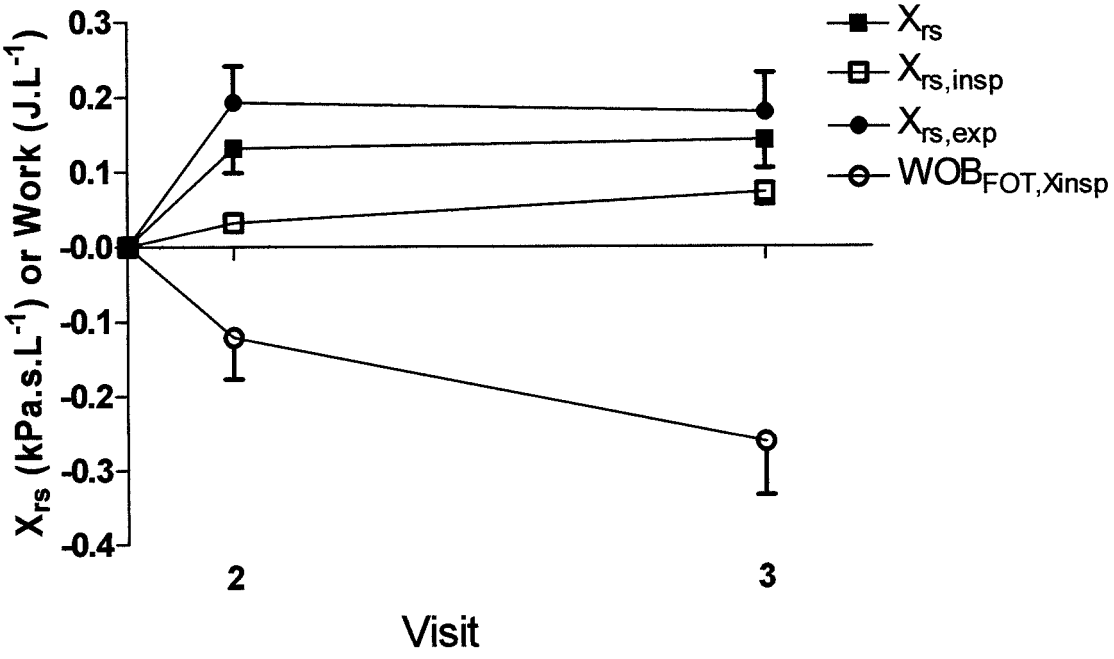
		Change (Visit 3 – Visit 1)	Coefficient of variation (%)	Sensitivity Index
Spirometry				
VC	**% change**	15.5	7.2	2.15
FEV_1	**% change**	24.8	9.6	2.58
IC	**% change**	16.7	8.8	1.90
Oscillometry				
R_{rs}	**% change**	-0.95	12.2	0.08
X_{rs}	**% change**	35.2	24.1	1.46
$R_{rs,insp}$	**% change**	-3.91	14.0	0.28
$X_{rs,insp}$	**% change**	27.4	17.6	1.56
$R_{rs,exp}$	**% change**	1.25	13.2	0.09
$X_{rs,exp}$	**% change**	37.1	28.6	1.30
$WOB_{FOT,Xinsp}$	**% change**	-40.5	27.1	1.49
%FL	**change**	-16.9	13.0	1.30

Figure 3.3.4. Time course of recovery of physiological variables for COPD subjects. (A) Volumes and flows (B) X_{rs} and $WOB_{FOT,Xinsp}$.
Values are change relative to visit 1. Error bars show SEM.

A)



B)



Correlation Between Physiological Variables and Symptoms

The correlation coefficients between changes in physiological variables and changes in symptoms or HRQOL were calculated for hypothesis generation purposes and are shown in Table 3.3.4.

Table 3.3.4. Pearson correlation coefficients showing association between changes (visit 3 – visit 1) in physiological variables and symptom and HRQOL scores

	FEV_1	VC	IC	PEF	P_aO_2	$X_{rs,insp}$	$X_{rs,exp}$	%FL	$WOB_{FOT,Xinsp}$
OCD	**0.500**	NS	NS	NS	**0.594**	**0.430**	NS	NS	**-0.406**
Borg	NS	NS	NS	NS	NS	NS	NS	NS	NS
TDI	**0.372**	**0.321**	NS	NS	**0.552**	**0.458**	**0.396**	**-0.402**	**-0.341**
LCADL	**-0.499**	NS	NS	NS	**-0.495**	**-0.408**	NS	NS	**0.481**
Mobility	NS	**0.428**	**0.329**	NS	**0.438**	**0.493**	**0.449**	**-0.410**	**-0.338**
SGRQ									
Activities	NS	NS	NS	NS	NS	NS	**-0.333**	NS	NS
Impacts	NS	NS	NS	NS	NS	**-0.420**	**-0.374**	**0.444**	**0.408**
Total	NS	NS	NS	NS	NS	**-0.442**	**-0.442**	**0.443**	**0.384**

Discussion

This study has demonstrated that improvement following an exacerbation of COPD can be detected either physiologically by spirometry, oscillometry or gas exchange or by following symptom scores or HRQOL (Table 3.3.2 and Figure 3.3.3). The majority of the improvement in all variables occurred within the first week of monitoring (Table 3.3.2 and Figure 3.3.4).

All the spirometric variables (i.e. FEV_1, PEF, VC, IC) increased significantly with the sole exception of FEV_1/VC which agrees with findings elsewhere[392-397]. One difference found here was that the size of the change was very consistent in terms of % predicted ranging from 11.0% for PEF to 12.1% for VC. This is at odds with the findings in the recent similar study by Stevenson et al. where the change in IC was found to be larger (19% predicted)[403]. The size of the change was much larger in the asthmatic subjects ranging from 17.8% predicted

for IC to 26.9% predicted for FEV_1. Significant changes of similar magnitude were seen in P_aO_2 for both COPD and asthmatic subjects (1.18 kPa vs. 1.64 kPa increase).

In the COPD subjects there were sizeable and significant increases in $X_{rs,insp}$ and $X_{rs,exp}$ (27.4% and 37.1%) and decreases in $WOB_{FOT,Xinsp}$ and %FL (-37.9% and –16.9%). As explained earlier, this can be interpreted physically as a decrease in both transpulmonary resistance and expiratory flow limitation during the study period. By comparison there was no change in $R_{rs,insp}$ and $R_{rs,exp}$ (% change –3.91% vs. 1.25%). The study by Stevenson et al. is the only previous report of longitudinal changes of forced oscillometry variables during an exacerbation of COPD or asthma[403] and this showed a strikingly similar pattern of change to that seen here. One difference was that the lack of change in R_{rs} was interpreted as implying that resistance does not improve during an exacerbation of COPD[403] but this inference can be contested. Firstly, in subjects with COPD, airway obstruction is present both during the exacerbation and after recovery. This may render changes in R_{rs} difficult to detect primarily because upper airway wall shunt weakens the relationship between transpulmonary resistance and R_{rs} when airway obstruction is present[404]. Secondly the fact that resistance does fall during recovery from an exacerbation is shown by the fact that there is a significant rise in FEV_1. According to the "equal pressure point" model described by Mead[268], flow at any lung volume increases if elastic recoil pressure rises or upstream resistance falls. The likeliest change in this scenario to produce the increased FEV_1 is a fall in airway resistance.

In the asthmatic subjects the largest changes were again seen in $X_{rs,insp}$ and $X_{rs,exp}$ (% change 47.6% vs. 96.0%). Absolute changes in $R_{rs,insp}$ and $R_{rs,exp}$ were also significant and much larger than those seen in COPD subjects. R_{rs} based variables may be relatively more useful in asthmatics because values of resistance approach normal after recovery and the masking effect of upper airway wall shunt would be reduced.

Changes in PTT only reached significance at visit 3 and changes in RWV were not consistent over the recovery period, increasing between visits 1 and 2 and decreasing between visits 1 and 3. In the COPD subjects there was a uniformly significant improvement in symptoms, ADLs and improvement in SGRQ (with the exception of the Symptoms score) confirming subjective recovery from the exacerbation. Significance of changes was more patchy in the asthmatic cohort reflecting the smaller sample size.

To compare the relative ability of spirometry and oscillometry to detect improvement during an exacerbation of COPD, the sensitivity index of each variable was calculated by dividing the change in the variable by its coefficient of variation (Table 3.3.3). This effectively estimated the variable's signal to noise ratio. It can be seen that spirometry was the superior measurement when reproducibility was taken into account. The coefficient of variation of the X_{rs} results could be improved by increasing the amplitude of the 5 Hz forcing signal, the duration of data collection or the number of times the measurement was repeated.

To assess the ability of changes in physiological variables to predict changes in symptoms or HRQOL, the correlation coefficients between changes in these variables from visit 1 to visit 3 were calculated (Table 3.3.4). The broadest association with symptomatic improvement was found for changes in FEV_1, P_aO_2, $X_{rs,insp}$ and $WOB_{FOT,Xinsp}$. Only changes in the oscillometry variables ($X_{rs,insp}$, $X_{rs,exp}$, $WOB_{FOT,Xinsp}$ and %FL) were associated with changes in HRQOL. Changes in PEF were not associated with symptom or HRQOL changes. Conversely, the symptom scales most broadly associated with physiological improvement appeared to be the TDI score and the VAS for mobility. Changes in Borg score were not correlated with physiological improvement.

A surprising aspect of the correlation analysis was the relatively weak association of change in IC with symptomatic improvement. Recently it was shown that, of resting pulmonary function tests following bronchodilator, change in IC was the strongest predictor of improvement in exercise capacity[405]. Also Stevenson et al.[403] found that patients reporting less breathlessness at the time of discharge were the ones in whom IC improved most during recovery. One factor contributing to this difference is that the patients in this study showed a slightly different pattern of physiological abnormality at baseline and change during recovery than seen in either of the two studies above. The patients here showed more of an obstructive picture (mean baseline FEV1: 0.96 L [43% predicted] compared with 1.03 L [47% predicted] [403]; mean change in FEV1: 0.274 L [11.4% predicted] compared with 0.20 L[403]) and less hyperinflation (mean baseline IC: 1.70 L [77% predicted] compared with 1.37 L [62% predicted][403]; change in IC: 0.295L compared with 0.42 L [19% predicted][403]). When combined with the inferior reproducibility (in absolute terms) of IC measurements, the biological noise in the measurements may have masked the association between change in IC and change in symptoms or HRQOL in this study.

Several difficulties were encountered in performing this study. Firstly, unless pre-exacerbation data are available there are no precise objective criteria for establishing when a patient has reached a stable state post-exacerbation. This was defined pragmatically here as a time point at least 6 weeks after visit 1 with the patient at home in what they deemed a stable condition and on normal medication. Secondly, it was difficult to achieve complete follow up with the type of subjects in this study due to chronic severe symptoms and the tendency to relapse. For clinical reasons, there was some variability in the exact time point at which the patients were assessed but the principle of assessing them at the beginning, early in recovery and then when largely back to stable state was achieved with reasonable success.

Conclusions

- Changes in parameters derived from X_{rs} (including $WOB_{FOT,Xinsp}$ and %FL) were easily detected during an exacerbation in both COPD and asthmatic subjects, were more widely associated with changes in symptom and HRQOL scores and could represent useful objective measurements for documenting recovery from an exacerbation. By contrast changes in $R_{rs,insp}$ and $R_{rs,exp}$ were small in COPD subjects and not useful in this context.
- Forced oscillometry is potentially an attractive and simple test to perform in these breathless patients because it is a passive manoeuvre requiring only tidal breathing. Spirometry does have superior signal to noise behaviour but by comparison with oscillometry is a maximal test which can be unpleasant to perform.
- The physiological changes seen during recovery from an exacerbation of COPD comprised both an improvement in operating lung volumes and a reduction in resistance (assessed by FEV_1 and X_{rs}).

4. Major Findings and Conclusion

The aim of this thesis was to develop and evaluate techniques for the non-invasive measurement of resistance, elastance and work of breathing.

The ability of forced oscillometry to predict R_L and W_{res} was investigated through histamine challenge tests in asthmatic subjects. The most important findings were:-

- X_{rs} measurements had a strong linear relationship with R_L and could predict its value more closely (using an appropriate linear regression model) than could oscillometry resistance (R_{rs}) values.
- As a consequence, a non-invasive method for measuring W_{res} was generated by combining inspiratory $X_{rs,insp}$ and $\dot{V}$.
- The linear relationship between $R_{L,insp}$ and $X_{rs,insp}$ appeared to be independent of the disease process.
- Lumped element modelling was able to explain this effect using a model which allowed central and upper airway wall shunting.

Two non-invasive techniques using positive pressure breathing delivered by modern CPAP and NIV technology were assessed as methods of measuring E_{rs} and WOB_{elas}.

- The CPAP method (initially proposed by Heaf and Prime in 1956) clearly showed superior performance and was the more promising candidate for further development.
- The NIV method could distinguish between subjects with normal and abnormal E_{rs} values but accuracy was not sufficient to separate gradations of abnormality.

Work validating the non-invasive measurement of intrinsic PEEP was not presented because limited data were ultimately available for this validation.

The new techniques were then evaluated in three clinical contexts. Firstly, changes in resting pulmonary function variables including forced oscillometry and derived work of breathing were compared with improvements in endurance exercise test performance during bronchodilator reversibility testing:-

- Bronchodilator produced measurable changes in plethysmography, oscillometry and exercise test parameters. Changes in RWV and PTT were non-significant or small relative to the errors in the measurement.
- Changes in resting IC and resistive parameters including $X_{rs,insp}$ were significantly associated with changes in $V_{E,end}$ but changes in these and $V_{E,end}$ were not associated with changes in T_{lim}. This suggested that the increased ventilatory capacity predicted by these changes in resting pulmonary function tests may not necessarily translate into improved exercise tolerance.
- Of the oscillometry variables, $\Delta X_{rs,insp}$ was most strongly associated with $\Delta V_{E,end}$, consolidating the suggestion that it is the optimum oscillometry choice for reflecting resistive change. Estimation of work of breathing by combination of $X_{rs,insp}$ and flow data conferred no advantage over the use of $X_{rs,insp}$ alone.
- There was a negative association between bronchodilator-induced increase in $V_{E,iso}$ and increase in T_{lim}, suggesting that reduction in ventilatory efficiency post-bronchodilator might be associated with poor improvement in exercise capacity.

Secondly, the ability of non-invasive E_{rs} and WOB_{elas} measurements to detect longitudinal trends in ILD was compared with conventional pulmonary function tests, exercise tests, symptoms and HRQOL. The results indicated that:-

- Longitudinal changes in $E_{rs,CPAP}$ and $WOB_{elas,CPAP}$ appeared to perform well at predicting the empirical progression score but this was not translated into an ability to predict survival.
- Endurance exercise tests (especially isotime variables and V_E/VO_2) and SGRQ scores proved superior longitudinal outcome measures for predicting survival relative to conventional tests such as VC and T_{LCO}.

Lastly, the ability of forced oscillometry and derived measurements (work of breathing and % flow limitation) to detect longitudinal physiological changes during an exacerbation of COPD was examined in comparison with spirometry, gas exchange, symptoms and HRQOL.

- Changes in parameters derived from X_{rs} (including $WOB_{FOT,Xinsp}$ and %FL) were easily detected during an exacerbation in both COPD and asthmatic subjects, were more widely associated with changes in symptom and HRQOL scores and could represent useful objective measurements for documenting recovery from an exacerbation. By contrast changes in $R_{rs,insp}$ and $R_{rs,exp}$ were small in COPD subjects and not useful in this context.

- The physiological changes seen during recovery from an exacerbation of COPD comprised both an improvement in operating lung volumes and a reduction in resistance (assessed by FEV_1 and X_{rs}).

In conclusion, the aims of this thesis, namely to propose, validate and evaluate techniques for the non-invasive measurement of respiratory mechanics were largely achieved. In particular the non-invasive measurement of work of breathing did prove possible with the techniques proposed and the accuracy of these methods was established. However, in the clinical scenarios studied, work of breathing did not add to the information already obtained from resistance or elastance.

There are several directions in which the work from this thesis could be developed. One of the most striking findings was the usefulness of inspiratory reactance to assess resistive properties in COPD subjects. When combined with the proven ability of expiratory reactance to indicate expiratory flow limitation (and thereby indirectly hyperinflation), this makes the forced oscillation technique a clear contender as an outcome measure in future trials of therapy for COPD. This would be true regardless of whether the intervention were pharmacological or mechanical (such as one-way valves, extra-anatomic stents, CPAP or NIV).

The techniques assessed for measuring elastance showed limited promise only. The NIV method is a complicated technique and there may be potential to improve it if further time were devoted to its development. In particular, the idea of applying higher inspiratory pressures to relax the respiratory muscles and then reduce the pressure for one breath is attractive and would be easily studied.

Finally, the use of endurance cardiopulmonary exercise tests as a longitudinal outcome measure in interstitial lung disease was particularly fruitful, with the ventilatory equivalent for oxygen standing out as the most sensitive indicator of poor survival. The use of isotime analysis in serial tests ensured that the subjects were compared after exactly the same workload in each test and provided an objective assessment of the subject's physiology at that time point. The findings in this group of ILD patients should be repeated in a larger cohort.

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Appendix 1. Technical Recommendations for Forced Oscillometry Measurements

The most recent statement of the technical requirements for forced oscillometry devices was written in 2003[20]. The principle points are summarised below and compared with the performance of the device used in this study.

1. *The FOT system should impose a load against spontaneous breathing of < 0.1 kPa.s.L^{-1} below 5 Hz.*

   This was not formally addressed with the device but subjects were able to breathe comfortably on the mouthpiece for several minutes.

2. *The pressure transducer across the pneumotachograph should have a common mode rejection ratio of at least 60 dB up to the highest frequency investigated.*

   This condition was satisfied[135]. Additionally, the phase difference between the FOT device flow and pressure signals was measured by looking at the system response to a 5Hz signal across a purely resistive load of 0.2 kPa.s.L^{-1} (Jaeger Toennies). The phase difference between the two signals was calculated from the phase of the cross power spectrum (see Chapter 1.2) and was found to be 0.1 ms (i.e. negligible).

3. *A peak to peak size of the forcing signal (P_{ao}) of 0.1 to 0.3 kPa is optimal. The largest P_{ao} should not exceed 0.5 kPa peak to peak*

   P_{ao} amplitude depended upon the load.

   - Load 0.2 kPa.s.L^{-1} – P_{ao} 0.08 kPa peak to peak
   - Load 0.38 kPa.s.L^{-1} – P_{ao} 0.11 kPa peak to peak
   - Load 2.0 kPa.s.L^{-1} – P_{ao} 0.2 kPa peak to peak

   Birch demonstrated reasonable results from any load where P_{ao} was >0.02 kPa [135]

4. *The flowmeter and the pressure transducer should be linear (within 2%) up to at least 1 L.s^{-1} and up to 0.5 kPa respectively.*

   The transducer used to measure P_{ao} was a piezoelectric single-ended gauge transducer with a range of ±2.5 kPa (Sensortechnics PXL0025DN50, Rugby, Warwickshire, UK). The linearity of this measurement was tested using an electronic pressure meter (Comark C9551, UKAS accredited calibration). The results are shown in Figure A1.1. Compared to the pressure meter, the absolute accuracy of the pressure transducer was within 24 Pa and 2%. Flow was measured using a heated Hans Rudolph screen

pneumotachograph with a range of ±160 $L.min^{-1}$ (HR3700A, Hans Rudolph Inc.). The pressure drop across the pneumotachograph was measured using a piezoelectric differential pressure transducer with a range of ±0.25 kPa (Sensortechnics PXL02X5DN). The linearity of the pneumotachograph was assessed using an electronic flow meter at flows above 0.25 $L.s^{-1}$ (Timeter RT200 Calibration Analyzer with Flow Module RT203, Allied Healthcare Products Inc., St. Louis, MO, USA) and standard rotameters at flows below 0.25 $L.s^{-1}$ (Gapmeter Laboratory Flowmeter Kit, Platon Flow Control Ltd, UKAS accredited calibration). The results are shown in Figure A1.2. Compared to the electronic meter, the absolute accuracy of the pneumotachograph was within 0.05 $L.s^{-1}$ and 4% except for two values at low flow rate (and hence low denominator which exaggerated measurement errors).

Figure A1.1. Plot demonstrating linearity of the pressure transducer used to measure pressure at the mouth in the FOT device.

a) shows transducer pressure, P_t, plotted against meter pressure, P_m. b) shows $\frac{(P_t - P_m)}{P_m}$ as a % plotted against P_m.

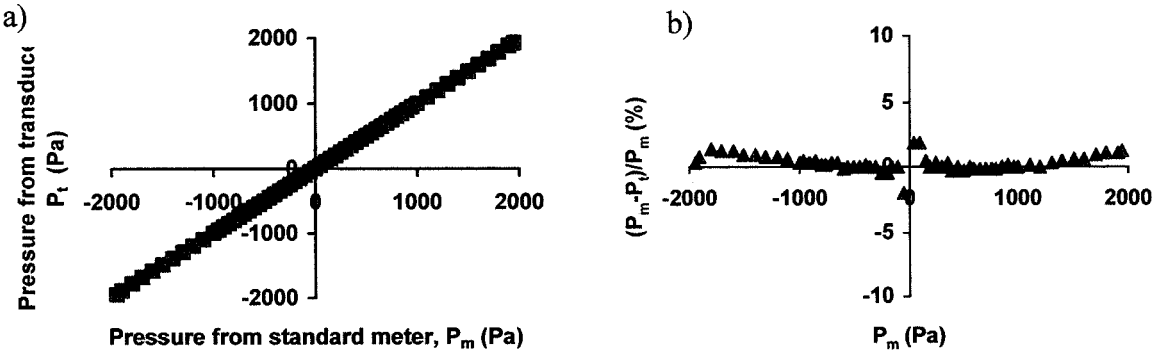
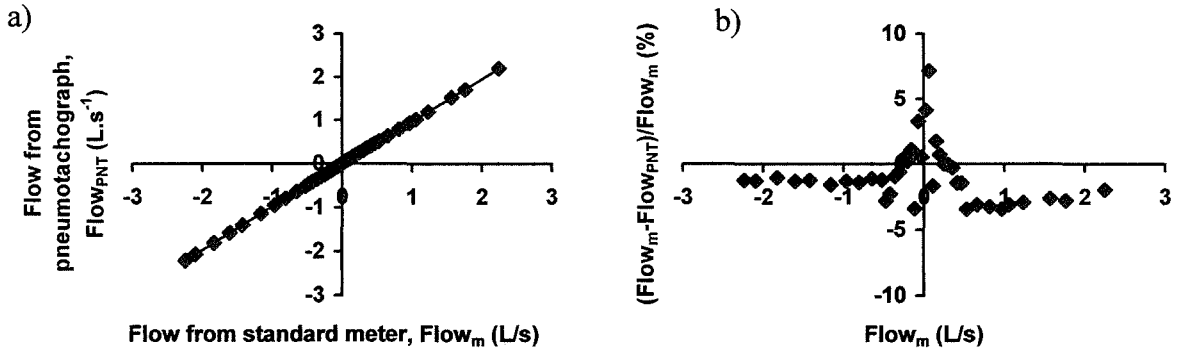


Figure A1.2. Plot demonstrating linearity of the pneumotachograph used to measure flow in the FOT device.

a) shows pneumotachograph flow, $Flow_{PNT}$, plotted against meter flow, $Flow_m$. b) shows $\frac{(Flow_{PNT} - Flow_m)}{Flow_m}$ as a % plotted against $Flow_m$.



5. *A reference impedance with a magnitude of ~1.5 kPa.s.L^{-1} is recommended. A maximum error of 10% or 0.01 kPa.s.L^{-1} is allowed.*

   Resistance calibration was performed using 3 resistors (0.2 kPa.s.L^{-1}, 0.38 kPa.s.L^{-1} and 2 kPa.s.L^{-1}) shown in Figure A1.3 and the summary results from all the calibrations are shown in Table A1.1.

Table A1.1. Measurements of calibration resistors

	Measured Resistance, R_{rs}	
Nominal Resistor Value	**Mean (kPa.s.L^{-1})**	**SD (kPa.s.L^{-1})**
0.2 kPa.s.L^{-1}	0.207	0.004
0.38 kPa.s.L^{-1}	0.387	0.004
2 kPa.s.L^{-1}	1.910	0.004

6. *Coefficient of variation is the main index of repeatability of Z_{rs} data. Reporting coherence is optional.*

   Coefficient of variation was used to analyse repeatability of our results.

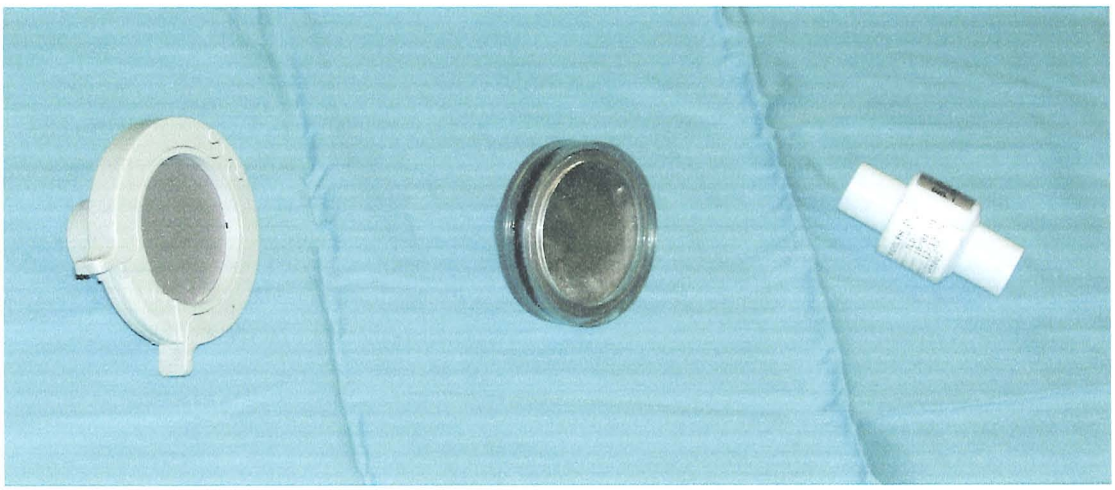
7. *The volume history of the subjects should be monitored for at least 30 seconds before the measurement is made.*

   This recommendation was followed.

8. *A total of 3 to 5 technically acceptable measurements should be performed.*

   In general two measurements of 1 minute apiece were performed and repeatability assessed on these.

Figure A1.3. Three calibration resistors used for the forced oscillometry device.
These were pure resistors with R_{rs} values of 0.2, 0.38 and 2.0 kPa.s.L^{-1}. Their origins (left to right) were Jaeger-Toennies, the Royal London Hospital Department of Clinical Physics and Hans Rudolph (Flow Resistance Standard R20, Hans Rudolph Inc.) respectively.



Appendix 2. Conversion from ATP to BTPS

Flow was converted from ATP to BTPS using the following equation[191,406]:-

$$\dot{V}_{BTPS} = \dot{V}_{ATP} \frac{(P_B - P_{H_2O})}{(P_B - 6.3)} \frac{310}{(273 + T_{amb})} \qquad \text{eqn A2.1}$$

where

$\dot{V}_{BTPS}$ is the flow under BTPS conditions

$\dot{V}_{ATP}$ is the flow under ATP conditions

P_B is the barometric pressure

P_{H_2O} is the partial pressure of water vapour at ambient levels of humidity and

T_{amb} is the ambient temperature.

P_B and T_{amb} were logged daily. Humidity was assumed to be 50%. The conversion to BTPS is necessarily an approximation because the exact conditions of the inspiratory and expiratory air were not known. Inspiratory air was a mixture of dry compressed air from a wall supply, the temperature of which was modified by the equipment tubing, and rebreathed air from the instrument head and tubing. The expiratory air had a different gas composition, the exact proportion of each gas changing as expiration continued. This altered gas viscosity which in turn altered measured flow as the pneumotachograph was calibrated with air. It can be calculated, however, that the error due to this effect was low (approximately 0.2%[406]). In addition, the temperature and humidity of expired air was different from inspired air, being closer to that seen under BTPS conditions and altered in an unpredictable way by the equipment tubing, the biological filter and the heated pneumotachograph. For a further discussion on the difficulties of this conversion see Miller[407].

From a pragmatic viewpoint, therefore, inspiratory and expiratory flow were corrected using the factor shown in equation A2.1, assuming inspiratory and expiratory gases were both at ATP.

Appendix 3. Volume Drift

The calculation of V by integrating $\dot{V}$ from a pneumotachograph introduced the problem of volume drift whereby V over time showed a negative or positive trend regardless of the zeroing accuracy of the pneumotachograph. This arose from several sources[191]:-[406]

1. the respiratory exchange ratio, i.e. the volume of expiratory air produced by metabolism differed slightly from the inspiratory air consumed
2. expiratory air was under different conditions of temperature and humidity from inspiratory air and therefore occupied a different volume
3. asymmetry of the pneumotachograph
4. zeroing error on the pneumotachograph
5. leaks from the pressurised mouthpiece during elastance measurements

Points 1 to 3 did not alter the points of zero flow but did alter the relative magnitude of inspiratory and expiratory flow whereas 4 to 5 altered the flow zero point. The preferred method of correction therefore depends on the relative contributions of these factors.

Since zeroing error was removed by calibration of the equipment and leaks were clearly identified during the measurements, the correction used in this study was chosen so as not to alter the zero points but rather to apply a scaling factor to reduce mean expiratory and increase mean inspiratory $\dot{V}$ or vice versa depending on the direction of the volume drift, as follows:-

$$k_I = 1 + \frac{\Delta V}{2\mu_I t_I} \qquad \text{eqn A3.1}$$

$$k_E = 1 - \frac{\Delta V}{2\mu_E t_E} \qquad \text{eqn A3.2}$$

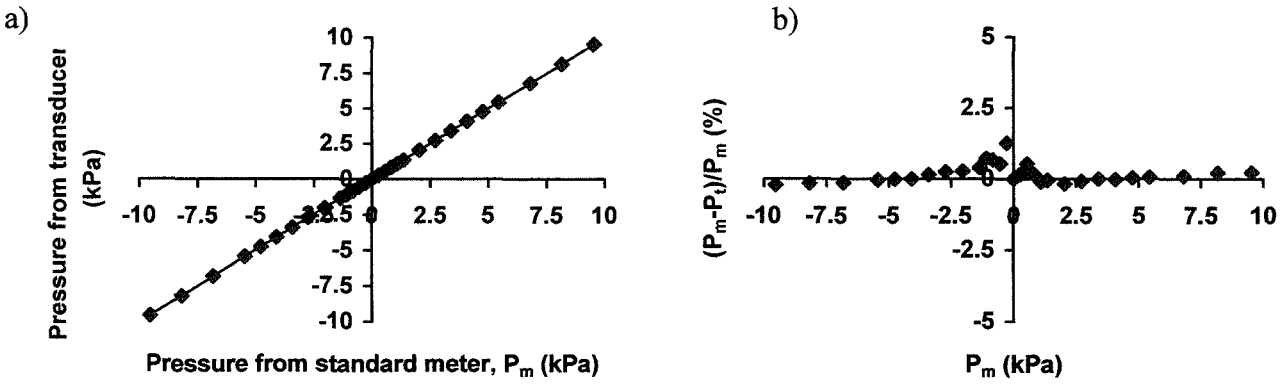
where k_I and k_E were the inspiratory and expiratory correction factors, ΔV was the volume drift over the measurement period, μ_I and μ_E were the mean inspiratory and expiratory flow rates and t_I and t_E were the total time spent in inspiration and expiration respectively. k_I and k_E were of mean value1.02 and 0.98.

Appendix 4. Technical Details of Balloon Catheter System

The linearity of the pressure transducers used with the balloon catheters was assessed over their working range using an electronic pressure meter (Comark C9551, UKAS accredited calibration) and the results are shown in Figure A4.1.

Figure A4.1. Plot demonstrating linearity of the pressure transducers used to measure P_{oes} and P_{gas}

a) shows transducer pressure, P_t, plotted against meter pressure, P_m. b) shows $\frac{(P_t - P_m)}{P_m}$ as a % plotted against P_m.



A key task in setting up this equipment was to determine the phase delay (i.e. the frequency response) between the pressure transducer in the FOT equipment and the balloon catheter/pressure transducer assembly. The equipment and technique used to assess frequency response from 0.5 to 24 Hz are illustrated in Figure A4.2. The relative amplitude and phase of the signals from the two transducers were determined using cross spectra (see Chapter 1.2) and the results shown in Figure A4.3. Using this technique, it was found that the time delay at 5 Hz between the pressure signals from the FOT transducer and the balloon catheter was 12 ms, increasing to 24 ms if an extension tube was used. These time delays were corrected in software. Note that the FOT equipment had been designed such that there was no measurable time delay between the FOT flow and pressure signals, a fact that was confirmed by looking at

the phase difference between the two signals when a purely resistive load (calibration resistor) was used. The time difference between the two signals was less than 0.1 ms.

In addition, the volume coefficient of displacement of the transducer was determined, this being the volume of air required to enter the transducer to generate a given pressure. Approximately, the ratio of coefficient of displacement to oesophageal compliance gives the percentage error in P_{oes} and was estimated in this case to be <0.1%[188] (assuming oesophageal compliance of 1.9 ml/mmHg[408]).

Figure A4.2. Equipment used to measure frequency response.
Sinusoidal signals of frequency 0.5 to 24 Hz were obtained sequentially from the signal generator and loudspeaker and were measured simultaneously by the FOT pressure transducer and the balloon catheter system. The differences between the two signals were analysed using cross-spectra to give relative amplitude and phase.

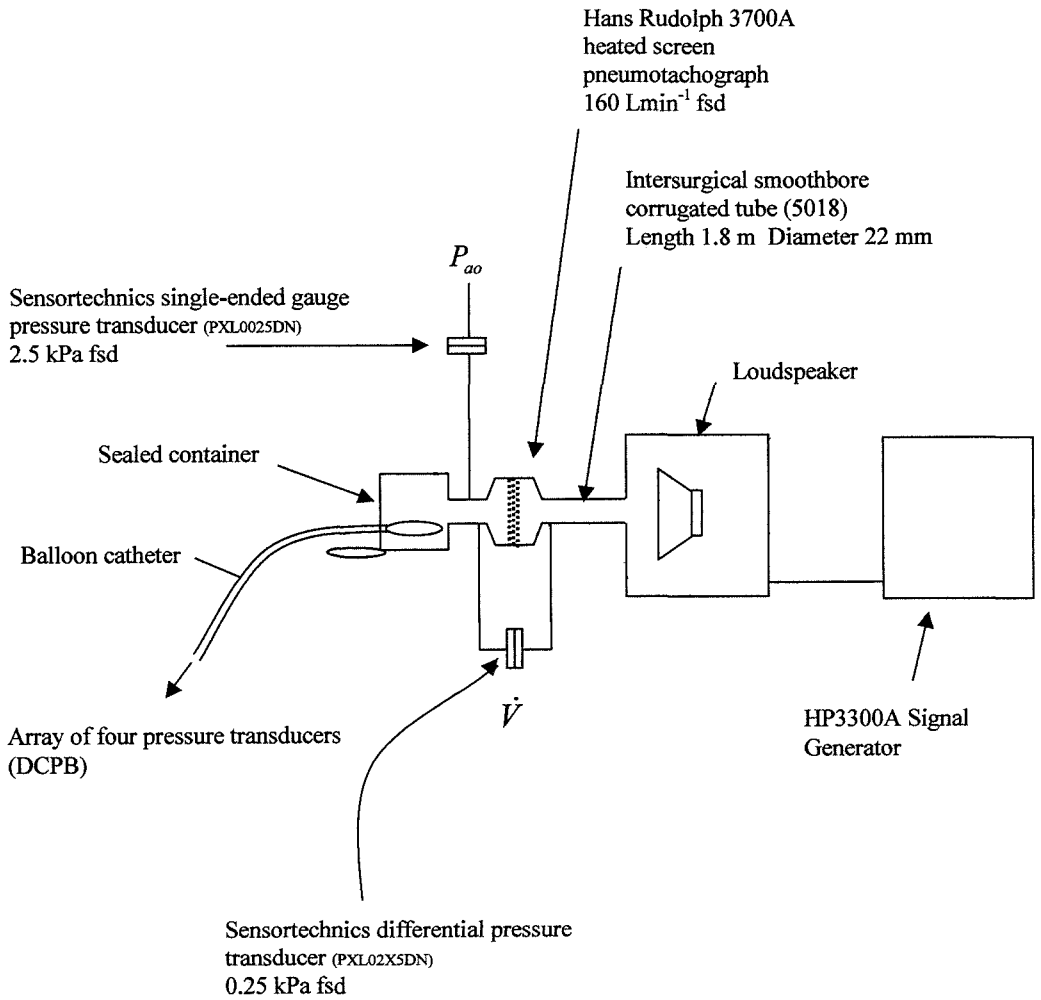
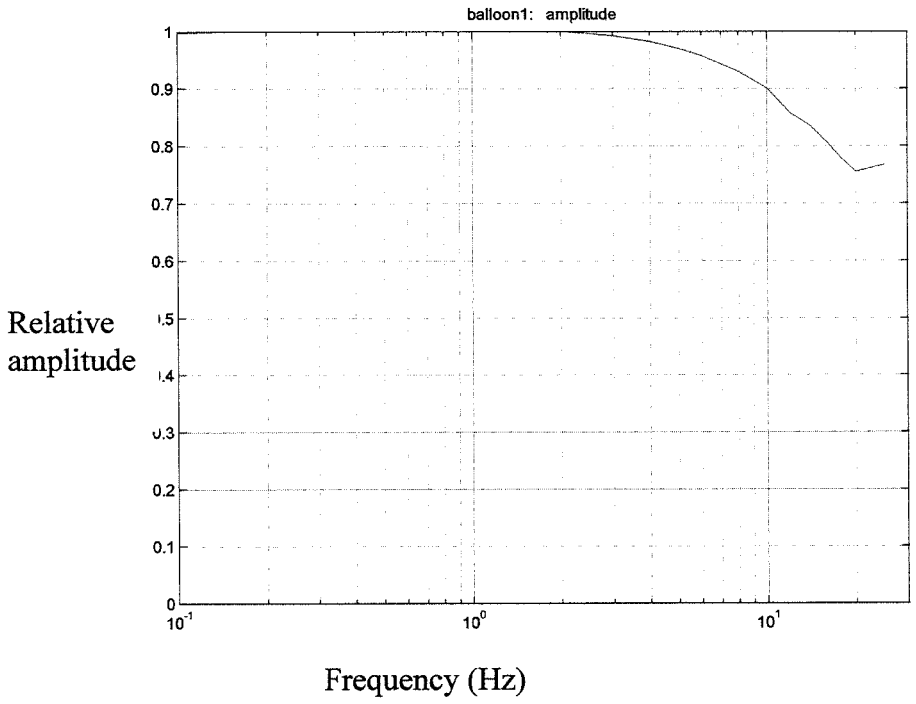
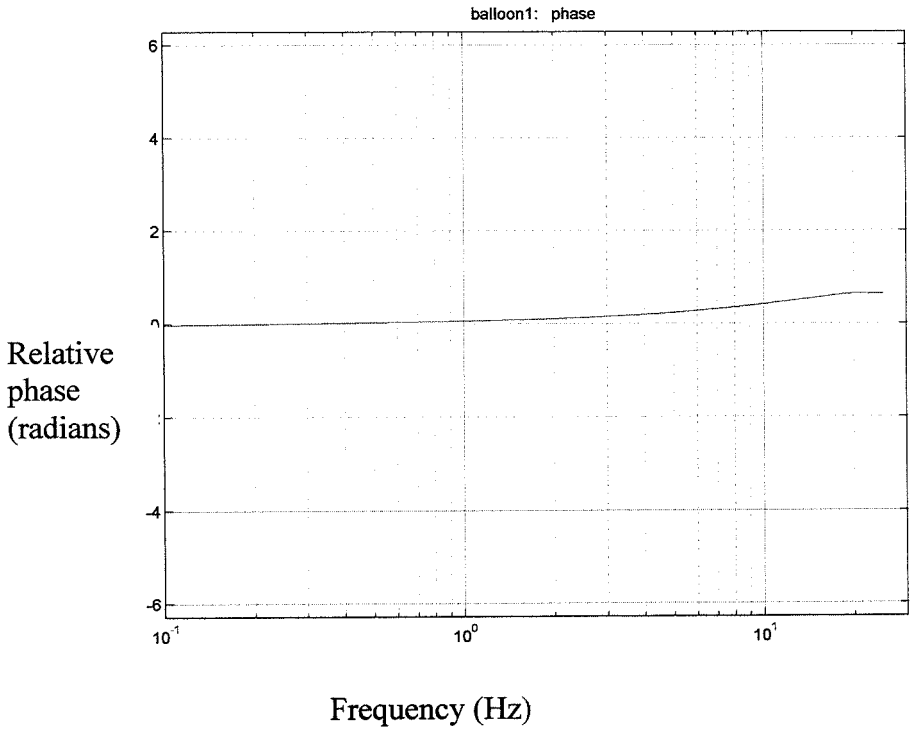


Figure A4.3. Frequency response of the balloon catheter pressure relative to the FOT pressure transducer a) Amplitude b) Phase.

A)



B)



Appendix 5. Lumped Element Model used for the Simulation of the Relationship between X_{rs} and R_L

Figure A5.1 shows the lumped element model used in the simulation. Z_{uaw} and Z_{br} represent the shunting effect of the upper and central airway walls respectively. Holding the cheeks was simulated by doubling the quoted value of Z_{uaw}[118]. Airway impedance was split into central (Z_c) and peripheral components. Two peripheral airway-tissue pathways (Z_{p1}, Z_{p2}) were included to allow for heterogeneous time constants. Z_w was the impedance of the chest wall and P_B barometric pressure. Z_{rs} was obtained from the following expression

$$Z_{rs} = \frac{Z_{uaw} \cdot Z_t}{Z_{uaw} + Z_t} \qquad \text{eqn A5.1}$$

$$\text{where } Z_t = Z_c + \frac{Z_{p1} \cdot Z_{p2} \cdot Z_{br}}{Z_{p1} \cdot Z_{p2} + Z_{p1} \cdot Z_{br} + Z_{p2} \cdot Z_{br}} + Z_w . \qquad \text{eqn A5.2}$$

The model neglected gas compressibility as this was unlikely to be a significant effect at 5 Hz and viscoelasticity was represented as a simple compliance included in the value of the peripheral compliance.

Representative values for the model components were obtained from the literature and are summarised in Table A5.1. In describing the model, compliance (the reciprocal of elastance) was used as this has been the convention in previous studies and thus values were easier to compare. Impedance (Z) for any component of the model was derived from resistance (R), inertance (I) and compliance (C) using the expression

$$Z = R + (\omega I - \frac{1}{\omega C}) \cdot i \text{ where } i = \sqrt{-1} \text{ and } \omega = 2\pi f . \qquad \text{eqn A5.3}$$

f is frequency. Z_{br} was assumed to be a pure compliance (C_{br}). The value often used for this parameter is 0.05 $L.kPa^{-1}$, this being the estimate made by Mead from changes in the volume of the anatomic dead space and airway transmural pressures[229]. In our model this value appeared to be too large as its original derivation included the entire dead space, it was greater than the measured compliance of the supraglottal airway wall (0.014 $L.kPa^{-1}$) and it produced simulation results which did not have the correct qualitative behaviour in either R_{rs} or X_{rs}. Several studies in which parameters were fitted to a similar model have estimated a smaller

value for C_{br} in the range 0.002 to 0.02 $L.kPa^{-1}$ [234,409,410] and hence a value in this range (0.005 $L.kPa^{-1}$) was used in the simulation.

Figure A5.1. The lumped element model used in the simulation.
Z_{uaw} and Z_{br} represent the shunts of the upper and central airway walls respectively. Airway impedance is split into central (Z_c) and parallel peripheral (Z_{p1}, Z_{p2}) components. Z_w is the impedance of the chest wall. P_{ao} is mouth pressure and P_B is barometric pressure.

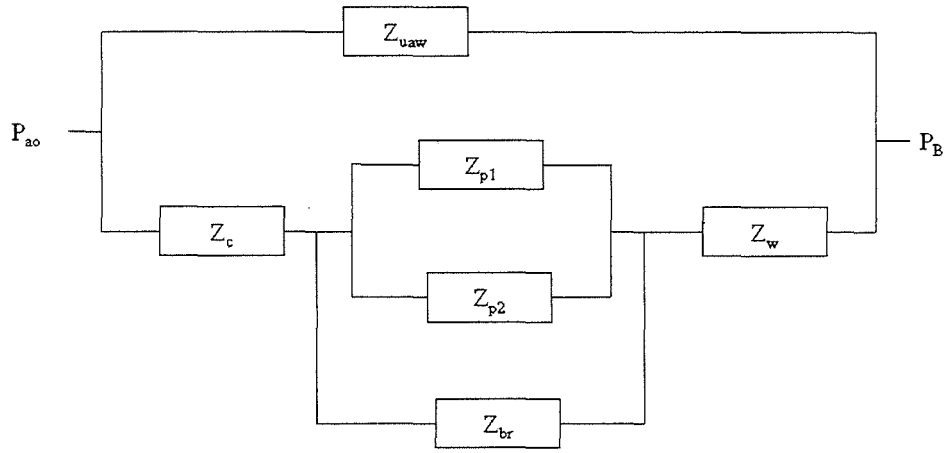


Table A5.1. Parameter values used in the lumped element simulations.

	Resistance (R) ($kPa.s.L^{-1}$)	Inertance (I) ($kPa.s^2.L^{-1}$)	Compliance (C) ($L.kPa^{-1}$)	Source
Z_{uaw}	0.8	0.0034	0.014	Peslin 1985 [411]
Z_c	0.07	0.002	-	Hantos 1986 [170]
Z_{p1}	see text	-	1.7	
Z_{p2}		-		
Z_{br}	-	-	0.005	see text
Z_w	0.05	-	0.5	Hantos 1986 [170]

To reproduce the effect of bronchoconstriction, the resistances of the peripheral airways (R_{p1}, R_{p2}) were increased from a baseline of $R_{p1} = R_{p2} = 0.2$ kPa.s.L^{-1} to a maximum combined value of 3.4 kPa.s.L^{-1}. Heterogeneous airways obstruction was created by increasing the value of R_{p2} whilst maintaining a fixed relationship between R_{p1} and R_{p2} as follows:-

$$R_{p1} = 5 \times R_{p2} - 0.8 \qquad \text{eqn A5.4}$$

where $0.2 \leq R_{p2} \leq 4$ kPa.s.L^{-1}. The peripheral compliance of 1.7 L.kPa^{-1} was divided equally between the two pathways. Repeating the simulation without either the upper or central airway wall shunt was achieved by removing Z_{uaw} and Z_{br} respectively. Removing the effect of parallel pathways was achieved by amalgamating Z_{p1} and Z_{p2} into a single pathway with a baseline resistance of 1 kPa.s.L^{-1} and compliance 1.7 L.kPa^{-1}. To simulate decreased static compliance of the lungs (stiff lungs) and chest wall (stiff chest wall), the values of compliance used to calculate Z_{p1}, Z_{p2} and Z_w were decreased by a factor of 5. To simulate more compliant lungs, compliance in Z_{p1} and Z_{p2} was increased by a factor of 5.