RESPIRATORY MUSCLE UNLOADING AND ENDURANCE EXERCISE PERFORMANCE

A Thesis

Submitted to the College of Graduate Studies and Research

in partial fulfilment of the requirements

for the Degree of

Master of Science

in the

Division of Biomedical Engineering

University of Saskatchewan

Saskatoon

By

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Saskatoon, Saskatchewan

February, 1992

Dedicated to

My beloved parents

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ACKNOWLEDGEMENTS

The author conveys his gratitude to his supervisor Dr. Charles Gallagher, for his valuable guidance and encouragement throughout the course of this work. Thanks are due to Trevor Zintel who helped with the technical aspects of the device set-up and also provided the software for data analysis in this study. The assistance of Dr. Colm McParland in conducting the experiments is appreciated. The author is thankful for the suggestions and recommendations of the advisory committee and the external examiner Dr. Nigel West, in the preparation of this thesis. The financial support received by the author from the Saskatchewan Lung Association and the College of Medicine is gratefully acknowledged. The author admits that if not for the encouragement (and patience !) of his family and friends (DH, AB, PB, MB, SR, AV, RV and many others), this achievement would not have been possible.

University of Saskatchewan

Biomedical Engineering Abstract # 92A358

Respiratory muscle unloading
and endurance exercise performance

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M.Sc Thesis Submitted to the
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ABSTRACT

Ventilatory demand increases throughout endurance exercise. It was hypothesised that if the normal loads on the respiratory muscles contribute to the limitation of endurance exercise, then a reduction of these loads (resistive unloading) should improve exercise performance. Inspiratory (I) and expiratory (E) unloading is possible at rest and moderate exercise levels, with the recent development of a feedback controlled loading/unloading device [Younes. *et al.* JAP 62:2491,1987]. This thesis is concerned with the specific modifications that were necessary in this device, to apply respiratory muscle unloading (FWUL) throughout the high ventilatory levels of prolonged exercise. The device was also used in a study in which seven healthy males performed constant load heavy exercise on two days, one with and one without (control) respiratory muscle unloading. With FWUL, mouth pressure was made positive with inspiration and negative with expiration proportional to flow, to provide a mean unloading of 1.7 $cmH_2O \cdot l^{-1} \cdot s$, effectively eliminating 73% of the total airflow resistance. The order of the two tests was randomised and they were separated by 4 days. The subjects exercised at high exercise levels ($\sim$90% maximum oxygen consumption) and flow proportional unloading was applied throughout these exercise levels. There was no significant difference (paired *t* test) in exercise duration between the control (mean ± SE, 11.4 ± 1.2 min) and FWUL (12.6 ± 2.1 min) tests. Repeated measures ANOVA revealed no difference in minute ventilation, tidal volume, respiratory frequency, heart rate and oxygen uptake, between the two tests. To confirm respiratory muscle unloading, intraoesophageal pressure (Ppl) was measured throughout exercise in 5 subjects. Respiratory muscle output (Pmus) was calculated by using Ppl and the measured values for chest wall elastic recoil, and normal values for chest wall resistive pressures. Peak and mean Pmus were significantly less with unloading (Δ(I) - 18%, 16%; Δ(E) - 36%, 37%, respectively), throughout exercise. The unloading device with its modifications was thus successfully used to unload the respiratory muscles at the high ventilatory levels of endurance exercise. The lack of improvement in exercise performance with unloading, in spite of a fall in respiratory muscle output, indicates that the normal resistive loads do not significantly contribute to endurance exercise limitation.

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Symbols	Description	Units
C	Compliance	$l \cdot cmH_2O^{-1}$
C_L, C_w, C_{rs}	Lung, Chest wall and Respiratory system compliances	$l \cdot cmH_2O^{-1}$
$C\bar{v}O_2$	Mixed venous O_2 concentration	$ml \cdot (100\ mg)^{-1}$
E	Expiration	
El	Elastance	$cmH_2O \cdot l^{-1}$
El_L, El_w, El_{rs}	Lung, Chest wall and Respiratory system elastances	$cmH_2O \cdot l^{-1}$
f	Breathing frequency	$breaths \cdot min^{-1}$
$F_{ET}CO_2$	End-tidal CO_2 concentration	%
FIO_2, $FICO_2$	Inspired O_2 and CO_2 concentrations	%
HR	Heart rate	$beats \cdot min^{-1}$
I	Inspiration	
K_1, K_2	Rohrer's constants	
K_L, K_t, $K_{t(e)}$	Constants relating pressure to Laminar turbulent and mixed flow	
P	Pressure	cmH_2O
P0.1	Occluded mouth pressure at 100 ms into the start of inspiration	cmH_2O
P_A	Alveolar pressure	cmH_2O
$PaCO_2$	Arterial partial pressure of CO_2	mmHg
Pao	Pressure at the airway opening	cmH_2O

Symbols	Description	Units
P_{bar}	Barometric pressure	mmHg
P_{BOX}	Pressure inside the body plethysmograph	cmH_2O
P_{elL}, P_{elW}	Elastic pressure across the Lung and Chest wall	cmH_2O
P_{ETCO_2}	End-Tidal partial pressure of CO_2	mmHg
P_I, P_{Imax}	Inspiratory and maximum pressures	cmH_2O
P_L, P_w, P_{rs}	Pressures across the Lung, Chest wall and the Respiratory system	cmH_2O
P_m	Mouth pressure	cmH_2O
P_{pl}	Pleural (oesophageal) pressure	cmH_2O
P_{plresW}, P_{plresL}	Pressure drop across the Chest wall and Lung due to flow resistance	cmH_2O
P_{SP}	Spirometer chamber pressure	cmH_2O
P_{STR}	Inspiratory muscle strength	cmH_2O
P_{TP}	Transpulmonary pressure	cmH_2O
$P_{\bar{v}CO_2}$	Mixed venous partial pressure of CO_2	mmHg
$\dot{Q}_c$	Pulmonary capillary blood flow	$l \cdot min^{-1}$
R	Resistance	$cmH_2O \cdot l^{-1} \cdot s$
R_{aw}, R_w, R_P	Airway, Chest wall and Lung tissue resistance	$cmH_2O \cdot l^{-1} \cdot s$
Re	Reynold's number	
T_I/T_{TOT}	Inspiratory duty cycle	
T_I, T_E, T_{TOT}	Inspiratory time, Expiratory time and total breath duration	s

Symbols	Description	Units
T_{LIM}	Inspiration muscles endurance time	minutes
$TT_{mus}(I)$	Tension-time index of the inspiratory muscles	
$\dot{V}$	Flow	$l \cdot s^{-1}$
V	Volume	l
$\dot{V}CO_2$	CO_2 output	$l \cdot min^{-1}$
$\dot{V}_I$	Inspiratory flow	$l \cdot s^{-1}$
$\dot{V}_{Imax}$	Maximal inspiratory flow	$l \cdot s^{-1}$
$\dot{V}_E$	Minute ventilation	$l \cdot min^{-1}$
V_{EE}	End-expiratory lung volume	l
$\dot{V}O_2$	Oxygen uptake	$l \cdot min^{-1}$ (STPD)
V_{SP}	Spirometer volume	l
V_T	Tidal volume	l

1. INTRODUCTION

1.1 Respiratory system

The respiratory system is one of the main links in the chain of oxygen transport and utilisation. The primary function of the respiratory system is to ensure adequate ventilation, gas exchange and oxygenation of the blood. The respiratory system is well designed to meet the demands of very heavy, short term exercise in the young untrained adult [Dempsey *et al*, 1980]. In normal healthy humans, maximal exercise is limited by cardiovascular (maximal stroke volume, cardiac output) and skeletal muscle (blood supply, oxidative capacity) factors [Saltin *et al*, 1983., Saltin, 1985]. A trained athlete has a greater maximal capacity than an untrained individual because of his/her increased cardiovascular and exercise capacity. Despite the increased exercise and cardiovascular capacities, etc., the pulmonary system in both the trained and untrained individual is quite similar in its gas exchange (diffusion) capacity.

The adequacy of the respiratory system's response to exercise may be limited by its gas exchange constraints and mechanical limitations. There have been many studies [reviewed by Bye *et al*, 1983] of the respiratory system's contribution to the limitation of heavy exercise. The demands made on the respiratory muscles are substantial during exercise. The increased metabolic needs require increased ventilation which is achieved by increasing inspiratory and expiratory flow rates. It is notable that an adequate ventilatory response is achieved during exercise with little changes in the mechanical characteristics (resistance, compliance) of the respiratory

pump. Massive increases (10 - 20 times) in ventilation are not uncommon during peak exercise in normal subjects. Presently, the available evidence suggests that the respiratory system in the untrained, young healthy adult is well adapted for the ventilatory demands of incremental exercise [Dempsey, 1985].

1.2 Thesis objectives

It has been hypothesized that the normal ventilatory load on the respiratory muscles could contribute to limitation of prolonged exercise [Younes and Kivinen, 1984]. If so, reducing the mechanical load on the respiratory muscles should increase exercise duration. Reduction of the load has been made possible with the recent development of a feedback-controlled loading/unloading device [Younes *et al*, 1987]. This device was used in the proposed study. The device generated positive or negative airway pressures in response to electrical command signals. The command signal (CS) in this study was airflow. Mouth pressure generated by this device was positive with inspiratory flow and negative with expiratory flow, resulting in resistive unloading of the muscles throughout the respiratory cycle. The object of this thesis was to adapt this device and its accessories to apply physiological unloading throughout prolonged exercise in normal subjects. A study was designed to examine if unloading of the respiratory muscles during exercise increased exercise tolerance. Intrapleural pressures were measured in five of the seven subjects to confirm whether unloading had actually occurred.

Chapter 2 of this thesis outlines the functional anatomy and the mechanical properties of the respiratory system. The physiological adjustments that take place during exercise are briefly explained. The available evidence regarding the role of

the normal ventilatory load in exercise limitation is presented. Alteration of the mechanical load on the respiratory pump has been frequently used to study the ventilatory response to the added load. A few of the techniques employed are reviewed in chapter 3. Chapter 4 details the principles of construction and operation of the feedback controlled loading/unloading device used in this study. The problems encountered and the modifications that were necessary to make this device operational for respiratory muscle unloading during heavy exercise are also discussed. Details of the experimental layout, the study design and the physiological measurements made are included in chapter 5. Chapter 6 discusses the results, their physiological and statistical significance. Chapter 7 provides a summary of the study and its conclusions.

2. MECHANICS OF VENTILATION

2.1 Introduction

Breathing, a rhythmic act consisting of an inspiration followed by expiration, is usually involuntary. It involves a volume of air entering the lungs and undergoing gas exchange. This basic function of the respiratory system is augmented during exercise due to the increased ventilatory needs. The anatomical design of the respiratory system and the various physiological adaptations that occur during exercise are described in this chapter. The internal chemical environment changes dynamically with the altered gas exchange requirements of exercise. The mechanical limits of the respiratory pump and the gas exchange requirements of the body have a role in exercise breathing pattern and ventilation. There has been growing interest into whether the normal loads on the respiratory pump contribute to the limitation of heavy exercise. It is possible that respiratory mechanical factors could directly or indirectly contribute to prolonged exercise limitation. A review of the available evidence that suggests the possibility is presented.

2.2 The respiratory pump - Physiology

2.2.1 Inspiration and expiration

The period of the breathing cycle includes the time for inspiration and expiration. The duty cycle of inspiration is physiologically important as it denotes that part of the total breath during which active contraction of the inspiratory muscles occurs. Minute ventilation is the total amount of gas moved in and out of the lungs in one minute and is the product of tidal volume (the volume of air in one breath)

and breathing frequency. There is evidence that the tidal volume and breathing frequency adopted at any given level of ventilation minimises the energy cost of breathing [Yamashiro and Grodins, 1973].

Breathing is effected by a host of respiratory muscles, chiefly the diaphragm and the muscles of the chest wall. Other less important contributors include the muscles of the neck and abdominal wall. These muscles become active during conditions of increased ventilatory need (e.g. exercise). The accessory muscles act by improving the mechanical advantage of the diaphragm and/or the rib-cage muscles [Grimby *et al*, 1976]. In addition to their indirect effects, the abdominal muscles can directly participate in active expiration thus reducing the end-expiratory lung volume. This improves diaphragmatic contractility by placing the muscle fibres at an optimal initial contracting length [De Troyer, 1984., Henke *et al*, 1988]. At rest, the process of breathing consists of an active inspiration initiated by the contracting diaphragm and the rib-cage muscles. The elastic energy stored during inspiration in all the contractile elements (lungs, chest wall, muscles) causes passive expiration. With the increased ventilatory needs during exercise however, all the respiratory muscles are recruited. With vigorous exercise, the expiratory muscles (e.g. abdominals) contract actively. This has a two fold advantage: (1) they improve ventilation by increasing expiratory flow, (2) they protect the inspiratory muscles from potential fatigue by improving their mechanical advantage [Henke *et al*, 1988]. The inspiratory muscles do not stop contracting at the end of inspiration; rather there is a gradual decrease in the number of contracting units so that the inspiratory muscles brake expiration in its early phases [De Troyer, 1984, Poon *et al*, 1987].

2.2.2 Lung volumes

The lungs and the chest wall are essentially visco-elastic structures arranged in series. Their individual static properties demand that each unit operate within its own elastic limit and in conjunction with the other. At any given lung volume, elastic forces exist across the lung and chest wall both at rest and during exercise. During quiet breathing there remains a volume of air in the lungs at the end of each expiration, the functional residual capacity (FRC). Excised lungs tend to collapse and assume a smaller volume due to the elastic forces in the lung connective tissue and the visco-elastic (surface tension) forces on the surface of each alveolus. On the other hand, the chest wall when it is freed, tends to expand. The distending forces (chest wall) and the collapsing forces (lungs) are balanced at FRC and the respiratory system is relaxed. The residual volume is the static volume of air that remains in the lungs after a maximal expiration. The volume of air in the lungs after a maximal inspiration is the total lung capacity (TLC). The difference between total lung capacity and residual volume is vital capacity (VC), which defines the limits of lung volume change. The interaction of the static forces across the lungs and chest wall is best illustrated by the pressure - volume diagram of the respiratory system (Figure 2.1, [Agostoni and Mead, 1964]). The elastic recoil pressure across the respiratory system (solid line) is the sum of the individual recoil pressures (broken lines) of the lungs and chest wall at that lung volume. The large arrows represent the elastic recoil of the lungs and chest wall. At FRC ($\sim$40% VC, figure 2.1), note that the distending and collapsing forces are equal.

The pleural cavity is a space between the lungs and the chest wall and is lined

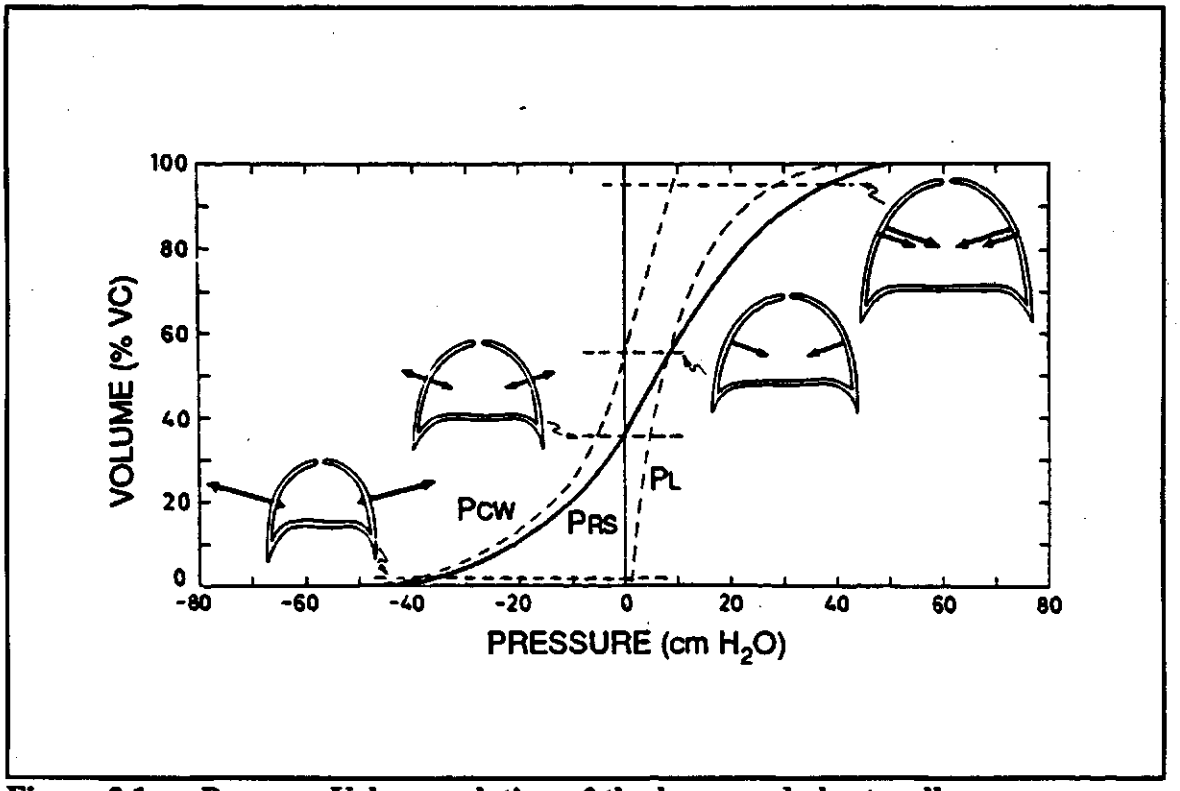

Figure 2.1: Pressure-Volume relation of the lungs and chest wall.

by the parietal (chest wall) and the visceral (lungs) pleural membranes. A thin (10 μm) film of fluid lining enables the parietal and visceral pleura to slide easily over each other and prevents them from separating. The sub-atmospheric pressure in the pleural space is due to the inward recoil of the lung tissue and the outward pull of the chest wall. During inspiration, the contracting muscles expand the chest cage and create a greater sub-atmospheric pleural pressure which inflates the lungs and causes air flow. As inspiration continues the elastic structures become taut resulting in no more change in volume and a cessation of flow.

2.2.3 Pressures in the respiratory system

The forces that generate air flow are differences in gas pressure which cause

changes in volume. Figure 2.2 illustrates these pressure gradients. The dynamic pressure exerted by the respiratory muscles serves to overcome the flow resistive and elastic recoil forces across both the lungs and chest wall and results in tracheal air flow. When the muscles are completely relaxed the pressure across the relaxed chest wall is Ppl (figure 2.2). Transpulmonary pressure (PTP) is the pressure gradient across the lung, i.e. between the alveolus and pleural space. These pressure gradients are usually small during spontaneous breathing at rest or during exercise. However, considerable pressures can be generated by maximal efforts against an occluded airway. The maximal pressures usually range -75 to -150 cmH_2O (inspiratory) and +150 to +200 cmH_2O (expiratory) in normal humans [Rochester, 1988].

2.3 Mechanical Properties

2.3.1 Static properties of the lungs and chest wall

Compliance - The elastic recoil properties of the respiratory system and its

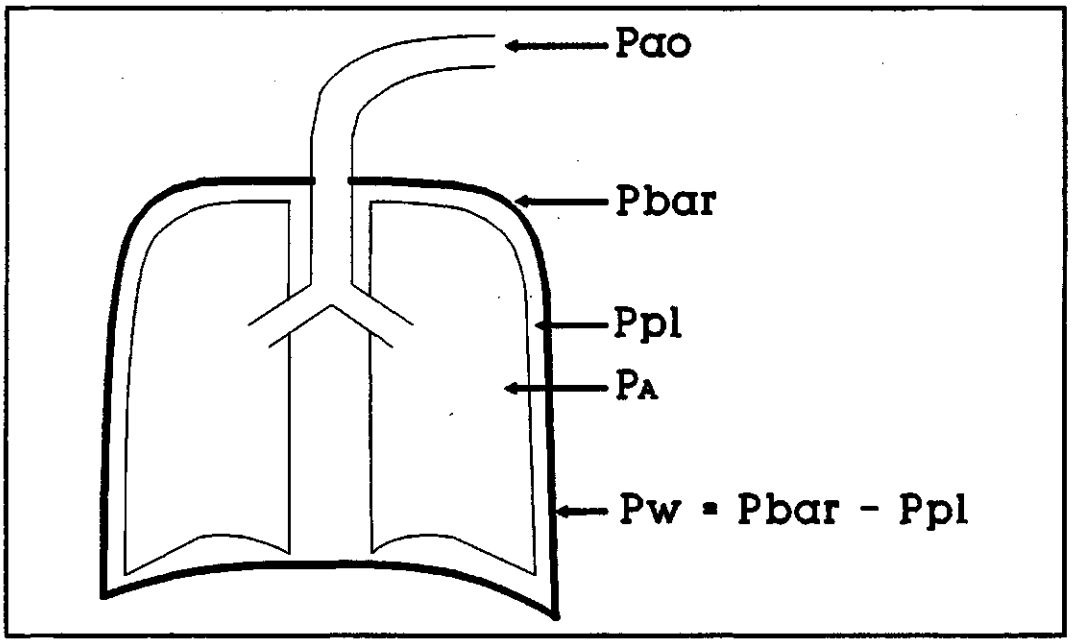

Figure 2.2: Pressures in the respiratory system.

components (lungs, chest cage) can be measured using the static relation between the volume and pressure changes. A typical method employed is the pressure-volume diagram of the respiratory system as shown in figure 2.1. The relation between changes in volume to changes in applied pressure is defined as the compliance of the structure.

$$C = \frac{\Delta V}{\Delta P} \tag{1}$$

Under normal conditions any change in the volume of the lungs must be associated with an equal change in the volume of the chest cavity; changes in volume are equal throughout the respiratory system. Static compliances of each of the components can be then calculated by relating their individual volume and pressure changes.

$$C_{rs} = \frac{\Delta V}{\Delta (P_A - P_{bar})}, \quad C_L = \frac{\Delta V}{\Delta (P_A - P_{pl})}, \quad C_w = \frac{\Delta V}{\Delta (P_{pl} - P_{bar})} \tag{2}$$

As the total pressure across the respiratory system (P_{rs}) is the sum of the pressures across the lungs ($P_{TP} = P_A - P_{pl}$) and the chest wall ($P_W = P_{pl} - P_{bar}$):

$$\frac{\Delta P_{rs}}{\Delta V} = \frac{\Delta P_{TP}}{\Delta V} + \frac{\Delta P_w}{\Delta V} \quad \text{or} \quad \frac{1}{C_{rs}} = \frac{1}{C_L} + \frac{1}{C_w} \tag{3}$$

The compliance of the respiratory system and its individual components depend significantly on the lung volume at which they are measured. This is because the individual P-V relationships of the lung and the chest wall are intrinsically non-linear. Note (figure 2.1) the non-linearity of the chest wall P-V relation, at low lung volumes (0 - 25% VC) and the non-linearity of the lung P-V relation at high lung volumes (> 90% VC). But as figure 2.1 illustrates, in the normal tidal volume range

(30 - 85% VC), the P-V relations of both the chest wall and lungs are linear [Agostoni and Mead, 1964]. Figure 2.3 shows the details of calculation of lung compliance during quiet breathing in one subject. Inspiratory flow and volume are negative. At the end of inspiration and expiration ($\dot{V} = 0$), there are no resistive pressure losses. Lung compliance is the ratio between the volume change and the difference in transpulmonary pressure at points of zero flow ($V_T/\Delta P_{TP}$) [Rodarte and Rehder, 1986].

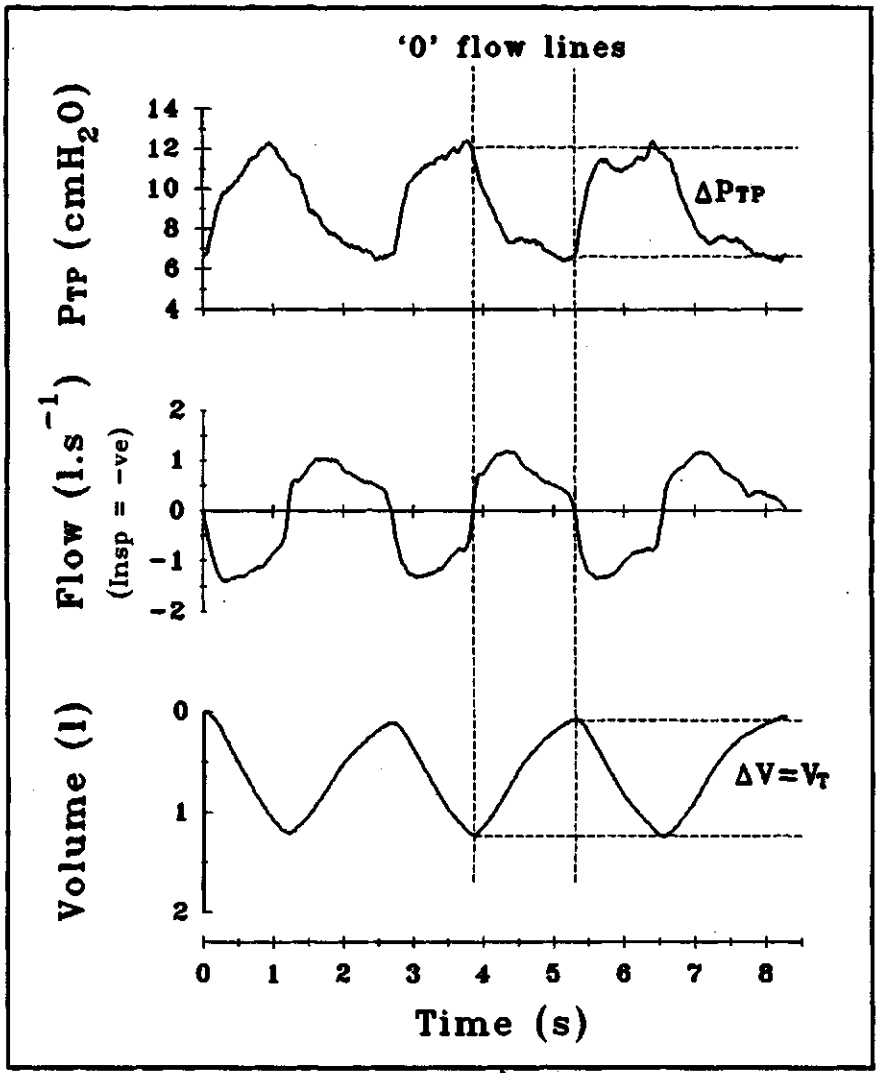

Figure 2.3: Relation between $\dot{V}$, V and P_{TP} during spontaneous breathing

Elastance - The reciprocal of compliance is called elastance, an index of the elastic recoil properties of the lung and chest wall. Hence $El_{rs} = \frac{1}{C_{rs}}$. The individual component elastances i.e. ElL and Elw are in series, Elrs = ElL + Elw. The elastic recoil pressure of the lung arises from two sources: tissue and visco-elastic surface forces. The tissue forces arise from the structural integrity of the lung and from the organisation of the collagenous and elastic fibres in the alveolar walls. The visco-elastic surface forces are generated by surfactant, a liquid lining the individual alveolar surfaces. The surface tension of surfactant is extremely low [Hildebrandt *et al*, 1979]. Surface tension forces also contribute to the overall non-linearity of the P-V curve of the lung. It has been shown that at low lung volumes, surface forces predominate while at higher lung volumes, tissue forces have a greater contribution to elastic recoil [Clements and Tierney, 1964].

2.3.2 Dynamic properties: Frictional resistance

Resistance to airflow is the ratio of the driving pressure to flow.

$$R = \frac{\Delta P}{\dot{V}} \qquad (4)$$

By measuring airflow and the measured pressure difference across the individual components of the respiratory system, we can obtain the flow resistance.

Airway Resistance - This is defined as the frictional resistance afforded by the entire system of air passages to airflow, from outside the body to the alveoli. Raw is calculated by the simultaneous measurements of flow and the pressure difference between the airway opening and alveoli. These variables can be measured accurately in a constant-volume variable-pressure body-plethysmograph [DuBois *et al*, 1956].

$$R_{aw} = \frac{P_{ao} - P_A}{\dot{V}} \qquad (5)$$

Pulmonary resistance - This is defined as the combined frictional resistance offered by the lungs (tissue flow) and the air passages. Pulmonary resistance is thus the ratio between the resistive pressure across the lung (Pao - Pplres) and flow. Pplres is the intrapleural pressure less the elastic pressure loss across the lungs (Ppl - PelL).

$$R_P = \frac{P\,ao - Ppl\,res}{\dot{V}} \qquad (6)$$

Lung tissue resistance can then be derived by subtracting Raw from RP .

Chest wall resistance - The frictional (viscous) resistance of the chest wall is determined by the simultaneous measurement of airflow and the pressure difference between the intrapleural space and the body surface. This pressure is corrected for losses due to elastic recoil of the chest wall.

$$Rw = \frac{(Ppl - Pelw) - P\,bar}{\dot{V}} \qquad (7)$$

The contributions of the individual components of the respiratory system to the total frictional resistance depends upon the individual anatomical structure and mechanical properties. Nasal breathing at rest changes to oral during exercise due to the increased resistance of the nasal passages with higher flows. Nasal resistance contributes a third of the total resistance during quiet breathing and is markedly non-linear with higher flows [Murray, 1986]. Resistances of the oro-pharynx and the trachea are also non-linear depending on the level of turbulence in these passages. Most of the resistance lies in the major and medium sized airways. Peripheral

airways, albeit smaller, contribute a very small amount to the total resistance because of their large number and parallel distribution. Resistance of the tracheobronchial tree is linear at flow rates of up to 2 $l \cdot s^{-1}$ accounting for ~60% of the airway resistance, the contribution of lung tissue being small [Murray, 1986]. Chest wall resistance accounts for 40% of the total respiratory system resistance during mouth breathing [Ferris *et al*, 1964].

2.4 The Lung in exercise

The pulmonary system is primarily concerned with ensuring adequate gas exchange at a minimal physiologic cost and cognitive effort [Dempsey *et al*, 1990]. A brief review of the system's response to exercise and some of the neuromechanical regulatory schemes that operate are presented in this section. The pulmonary system is ideally designed and regulated to meet the homoeostatic demands of very heavy, short term aerobic exercise in a normal healthy adult [Dempsey *et al*, 1980]. Some of the major demands imposed on the healthy pulmonary system during exercise, as dictated by an increase in O_2 consumption and CO_2 production are shown in table 2.1 [Dempsey *et al*, 1990]. The increased work of the skeletal muscles during exercise results in increased O_2 consumption and CO_2 production. Efficient gas exchange is required at the alveolus-gas interface to maintain homoeostatic conditions during maximal exercise. The amount of time spent by the desaturated haemoglobin molecule at the blood-gas interface becomes less and less due to increased blood flow through the lungs. The control system, monitoring these demands has to efficiently and closely interrelate the magnitude and the pattern of responses, at a minimum energetic cost to the lung and chest wall.

Table 2.1. Demands on the pulmonary control system

Description	Parameter	Untrained Normal "athletic" adult			Trained Athlete	Units
		REST	MILD	MAX	MAX	
Metabolic demand	$\dot{V}O_2$	0.3	1	3	5	$l \cdot min^{-1}$
Gas exchange constraint	$C\bar{v}O_2$	15	11	6	<2	$ml(100\ ml)^{-1}$
	$P\bar{v}CO_2$	46	52	65	>75-80	mmHg
Response	$\dot{V}E$	5	25	90	140	$l \cdot min^{-1}$
	$\dot{Q}c$	5	11	20	27	$l \cdot min^{-1}$

The responses include exercise hyperpnea (increased VT and/or f), increased mechanical work of breathing and efficient gas exchange [Dempsey *et al*, 1990]. The integration of these responses is dependent on information inputs (feed-forward and feedback) provided to the controller. The controller is informed of the increased rate of CO_2 production and the increasing rate and force of skeletal muscle contraction. The effective coordination of these inputs requires error-detection. Figure 2.4 outlines the feedback control and the general scheme of integration of responses by the respiratory controller [Dempsey, 1985]. The most important sources of feedback are: information about mechanical (impedance) changes proportional to $\dot{V}$, V and P from (*1*) chest wall and skeletal muscles; (*2*) stretch receptors in the lung, airway and chest wall, and chemical information about P_{CO_2}, P_{O_2} and arterial pH from (*3*) peripheral and central chemoreceptors.

The control system is also informed of the dynamically changing load patterns and ventilatory requirements during exercise in order to optimize respiratory muscle effort. Some of the evidence available attests to this fact. $\dot{V}E$ is maintained by a

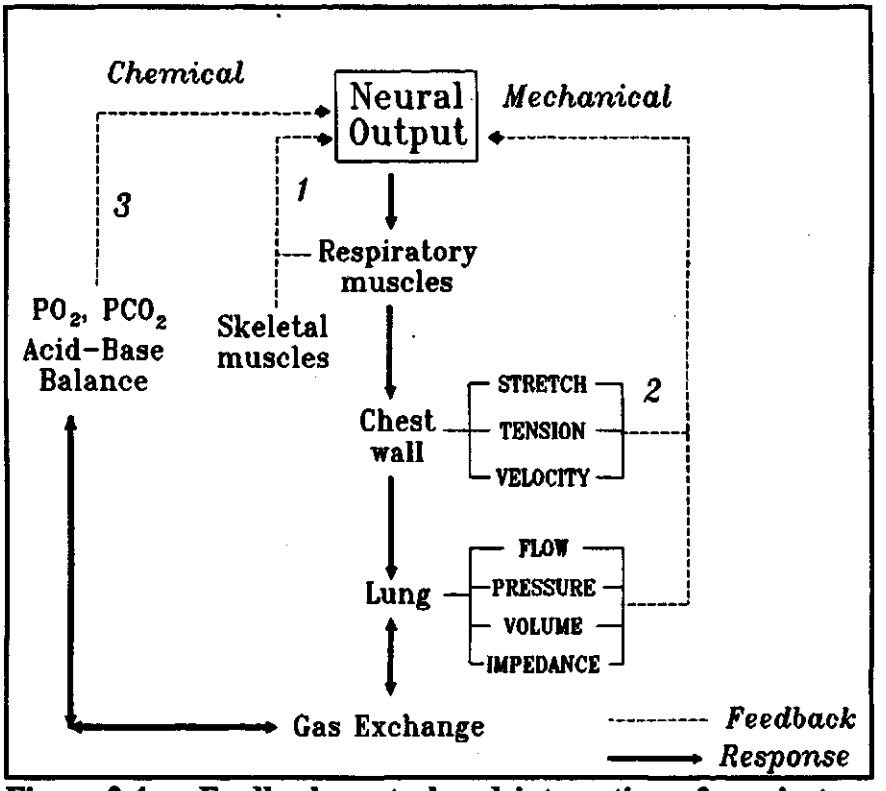

Figure 2.4: Feedback control and integration of respiratory responses.

tight balance between f and VT, so as to maintain VT within the linear limits of the P-V curve (max VT < 60% VC, figure 2.1) [Dempsey *et al*, 1980]. Accessory muscle recruitment occurs even during mild exercise [Grimby *et al*, 1976]. Expiration, usually passive at rest, becomes predominantly active due to expiratory muscle recruitment, a process that accelerates expiratory flow and allows inspiration to be completed in the available time during exercise thus preserving TI/TTOT. Active expiratory muscle contraction can actually aid the diaphragm in its subsequent inspiratory contraction by putting it in a more favourable length-tension relationship [Henke *et al*, 1988]. Sudden relaxation of the expiratory muscles at the end of expiration results in a slight negative pressure inside the thorax, a process that can aid negative pressure to build faster during a short inspiratory time [Grimby *et al*, 1976]. It is possible that the

recruitment of expiratory muscles during exercise spares the inspiratory muscles some work by improving their mechanical advantage thus postponing the onset of fatigue.

2.5 Does the respiratory system limit exercise performance ?

In recent years it has been suggested that respiratory muscle function may contribute to the limitation of exercise in normal healthy humans [Bye *et al*, 1983]. It has long been recognised that the ability of the respiratory muscles to sustain high levels of ventilation is limited [Leith and Bradley, 1976., Tenney and Reese, 1968], and the highest levels of ventilation possible can be maintained only briefly. Because exercise ventilation can be a large part the subject's maximum ventilatory capacity, it is possible that respiratory muscle fatigue might influence endurance. This section reviews some of the neuro-mechanical evidence regarding the possibility of respiratory factors limiting prolonged exercise.

The diaphragm can be fatigued by breathing against resistive loads [Roussos and Moxham, 1986]. Respiratory muscle function during resistive loading has been studied by many authors. The two main determinants of respiratory muscle fatigue are the ratio of inspiratory muscle pressure (PI, demand) to the maximal pressure (PImax, capacity) and the duty cycle of the inspiratory muscles. The product (PI/PImax· TI/TTOT) is often called the tension-time index [Bellemare and Grassino, 1982] and defines the intensity and the duration of contraction of the inspiratory muscles. The rate of muscle contraction, i.e. the ratio of velocity of contraction to maximal velocity is another important determinant during spontaneous breathing [Fitting, 1991]. It has been shown that the tension-time index of the inspiratory muscles at the end of maximal incremental exercise is at or close to the critical

tension-time index associated with inspiratory muscle fatigue [Younes and Kivinen, 1984].

Respiratory muscle fatigue could contribute to the limitation of maximal exercise indirectly by increasing the sensation of dyspnea, thus increasing the overall discomfort of exercise. It is possible that the increasing metabolic requirements of the respiratory muscles during exercise could result in blood supply being diverted from the exercising limb muscles, thus contributing to earlier limb muscle fatigue. It has been demonstrated that maximal exercise ventilation equals approximately 70% of maximum voluntary ventilation ($\dot{V}E/\dot{V}E_{max}$) [Bye *et al*, 1984]. $\dot{V}E_{max}$ *per se* cannot be maintained longer than 15 - 20 seconds and so the level of spontaneous ventilation that can be maintained during prolonged heavy exercise (15 - 20 minutes) is much less (closer to 55 - 60% $\dot{V}E_{max}$).

Different techniques have been used to look for evidence of respiratory muscle fatigue during maximal exercise. Using oesophageal electrodes, electromyographic evidence (a fall in the high to low frequency ratio) consistent with diaphragmatic fatigue has been demonstrated [Bye *et al*, 1984] during and towards the end of submaximal constant-work exercise. While these changes are consistent with fatigue, recent studies [Bazzy *et al*, 1986] indicate that they are not specific to fatigue. Other studies [Bye *et al*, 1984., Loke *et al*, 1982], using trans-diaphragmatic or peak (most negative) mouth pressures, have reported a reduction in inspiratory muscle strength immediately after endurance exercise. Although these findings are suggestive of respiratory muscle fatigue, they are not conclusive because of the high degree of motivation required to perform these maximal manoeuvres, especially following

exhausting exercise. Animal studies provide further evidence that the respiratory muscles may be contracting at maximal levels. Diaphragmatic glycogen stores have been found to be depleted during prolonged exercise in rats [Fregosi and Dempsey, 1986., Ianuzzo *et al*, 1987]. At end exercise in ponies, vasodilatation in the diaphragm has been found to exceed that of the myocardium [Manohar, 1986]. These results although not conclusive, are indicative that the respiratory muscles are performing at or near maximal capacity at end exercise. The progressive recruitment of accessory expiratory muscles during the course of heavy exercise aids in improving inspiratory muscle efficiency and possibly postpones the onset of fatigue. The role of respiratory muscle fatigue in exercise limitation is thus not clearly defined.

2.6 Summary

A brief overview of the structural and functional characteristics of the respiratory system was presented. The function of the respiratory pump during exercise is determined both by its mechanical limits and the ventilatory needs. The ventilatory reserves and the efficient adaptability of the respiratory system indicate that the pump is well suited to exercise. During heavy exercise, it is unlikely that the metabolic requirements of the other organ systems significantly exceed the ventilatory and blood:gas matching capacities of the respiratory system. However some available evidence suggests that respiratory mechanical factors could play a role in exercise limitation.

3. ALTERATION OF THE LOAD ON THE RESPIRATORY SYSTEM

3.1 Introduction

The response of the respiratory system to exercise is influenced by its mechanical properties. The focus of this chapter is the role of the normal intrinsic load in determining the exercise ventilatory response. The respiratory system has the ability to make adjustments during exercise, but these adjustments are limited by the structural characteristics and geometrical arrangements of the ventilatory pump. These mechanical factors will not only determine maximal ventilatory performance but also influence the efficiency of gas exchange at levels well below these maximal limits [Ward *et al*, 1982]. The mechanisms that operate and the overall adjustments that take place with the increasing ventilatory levels depend on the type and the intensity of exercise. They have been examined by using various experimental techniques that deliberately changed either the mechanical properties of the lungs and chest wall, the resting lengths of the respiratory muscles, or the load against which the respiratory muscles operated. Alteration of the mechanical load against which the respiratory muscles operate has been a useful technique in understanding the control of breathing in humans [Cherniack and Altose, 1981]. The methods used are of 2 types; ventilatory loading or unloading. Some of the responses to ventilatory loading and the physical principles involved in unloading are reviewed in this chapter.

3.2 Ventilatory loading

The immediate and the long term ventilatory responses to an added load in series with the respiratory pump, enables a better understanding of the mechanical

adjustments that take place in the respiratory system. Loading can simulate various disease states during which the respiratory muscles operate against an increased load. Some of the commonly used ventilatory loads are:

Elastic: These are loads that change the pressure-volume response characteristics of the respiratory system. This is because the added load is in series with the lung and chest wall. Elastic loading necessitates a greater pressure change for a given change in lung volume. External elastic loading is effected by breathing from a rigid sealed container or by chest strapping [Freedman and Weinstein, 1965].

Flow Resistive: These are loads that affect the pressure-flow relationships. Flow-resistive loading results in a fall in flow rate for a given driving pressure. It can be accomplished by breathing through high resistance devices (tubes of small diameter, perforated disks etc.) or by increasing the density or viscosity of respired gases [Flook and Kelman, 1973., Burdon *et al*, 1982]

Pressure: Continuous positive or negative pressure applied at the mouth serves to load the respiratory muscles. This can also change the elastic and resistive properties of the chest wall and lung by changing the resting VEE [Grassino *et al*, 1973].

Threshold loading: These are pressure loads that prevent flow at the beginning of inspiration or expiration until a threshold pressure is reached. These cause an isometric contraction of the respiratory muscles until a critical pressure is reached, when air-flow begins. Breathing from a closed container in which the inlet tube dips a predetermined distance in water in the container is one example of threshold loading [Freedman and Weinstein, 1965].

External ventilatory loading has been used to study the immediate and

sustained mechanical adjustments that take place in the respiratory system following the imposition of the load. It has been used to delineate the roles of chemical and mechanical factors in ventilatory control. By applying a specific type of load it has also been possible to understand the effects of specific mechanical derangements that occur in certain disease states (e.g. resistive loading to simulate chronic airways disease).

3.2.1 Effects of loading on ventilatory responses to exercise

The work done by the respiratory muscles depends on the mechanical properties of the chest wall and the lungs and on the pattern of breathing. For instance, if an elastic load is imposed the ventilatory work done by the respiratory muscles can be maintained if V_T is kept small and a rapid shallow breathing pattern is adopted. Early studies [Yamashiro and Grodins, 1973] have revealed that given the size and the mechanical characteristics of the lung and chest bellows, there are certain breathing frequencies at which respiratory work is reduced. These frequencies are dependent on V_{EE} (at rest and during exercise) as well as the pattern of airflow.

Ventilatory loading at rest tends to modify the relation between V_T and f, or V_T and $\dot{V}$, primarily to minimise respiratory work and optimise gas exchange. With the higher levels of ventilation during exercise, adjustments to mechanical loading favour a reduction in the work of breathing [Cherniack and Altose, 1981]. Normally during exercise V_T and f increase until V_T reaches a plateau. Further increases in $\dot{V}_E$ result from increasing f [Gallagher *et al*, 1987]. Elastic loading reduces vital capacity and thus decreases the maximal V_T reached during exercise. Ventilation is then

achieved by rapid, shallow breathing. Inspiratory resistive loading [Flook and Kelman, 1973] caused a significant fall in f and a fall in VT was found only at higher exercise levels. In contrast, breathing low density gas mixtures resulted in an increased f and an unchanged VT [see below]. During incremental exercise of increasing intensity, it was demonstrated that flow-resistive loading progressively reduced maximal $\dot{V}_E$, f and exercise performance [Demedts and Anthonisen, 1973]. Doubling the resistance did not have any significant effect on the above variables. Moderate to severe resistance to airflow (4×, 10×) however had a significant effect in depressing ventilation (up to 50% with 10×). Abrupt imposition of these loads resulted in immediate changes due to a fall in VT, which reached a new steady-state value later [Demedts and Anthonisen, 1973].

Respiratory responses to ventilatory loading therefore depend on the type, severity and the state (rest *vs* exercise) during which the load is applied. The sum total of the responses during exercise appears to be as a result of a compromise between the mechanical and the neuro-chemical adjustments that occur during exercise.

3.3 Ventilatory unloading

Increasing the load against which the respiratory muscles operate was shown to reduce ventilation and modulate the response to ventilatory stimuli, as described in the previous section. Unloading the respiratory muscles during exercise provides more information about the effects of the normal loads in the respiratory system and their role in exercise performance. This section deals with two methods that have been used to apply resistive unloading to the respiratory muscles: (1) density

dependent unloading and (2) mechanical assistance devices.

3.3.1 Density dependent unloading

Resistance to airflow is an important determinant of the mechanical impedance of the respiratory pump especially during exercise, as the high ventilatory demand necessitates greater flow rates. This section deals with some of the physical principles involved in the flow of gas through the large and small airways, and the use of low-density gas mixtures to apply resistive unloading of the respiratory muscles.

The flow of gas through a tube of constant cross-section is laminar below a critical velocity and turbulent above it. Turbulent flow is present in the major air passages when Reynold's number (Re) exceeds 2000 [Murphy *et al*, 1969]. Re is a dimensionless quantity used to relate the physical properties of the gas (density, viscosity) to the structural (diameter) and flow (velocity) characteristics in the tube (ratio of inertial to viscous forces).

$$\text{Re} = \frac{\text{density} \times \text{velocity} \times \text{diameter}}{\text{viscosity}} \qquad (1)$$

$$\text{or,} \quad \text{critical velocity} = \frac{\text{Re}(2000) \times \text{viscosity}}{\text{density} \times \text{diameter}} \qquad (2)$$

The driving pressure required to move air through a smooth, non-branching tube of constant diameter is a function of gas viscosity, $\dot{V}$ and the length and radius of the tube [Slonim and Hamilton, 1981]. When airflow is laminar, ΔP varies linearly with $\dot{V}$.

$$\Delta P = K_L \cdot \dot{V} \qquad (3)$$

The constant K_L , is dependent on the density and viscosity of the gas as well as airway geometry. However, with turbulent flow (Re > 2000) in a smooth unbranching airway with a constant diameter:

$$\Delta P = K_t \cdot \dot{V}^{1.75} \quad (4)$$

where K_t, a new constant, depends on the physical characteristics of the gas, the geometry of the airway and is also dependent on a friction factor ($0.0791 \cdot Re^{-0.25}$). In the lungs, where the airways are not smooth, but also branch and change directions abruptly and have varying cross-section, a higher degree of turbulence is prevalent. Then,

$$\Delta P = K_{t(e)} \cdot \dot{V}^2 \quad (5)$$

where $K_{t(e)}$ now takes into account the physical characteristics of the gas and the geometry of the airway. With increased turbulence (Re > 10000) the friction factor becomes negligible. The mechanical energy losses in the airway are all functions of $\dot{V}$ and occur simultaneously throughout the airway, from the nasal passages down to the terminal bronchioles. Flow is either laminar or turbulent at any point in the airway depending on airway geometry. In the periphery of the lungs airway diameters are small but the total cross-sectional area is large, because of their large number. Gas velocities become progressively slower towards the periphery. Pressure losses in the periphery are predominantly due to viscous forces ($\Delta P = K_L \cdot \dot{V}$). In the more central airways, although the individual diameters are large, their total cross-sectional area is less than that of the peripheral airways. Pressure loss in these airways is predominantly due to turbulence ($\Delta P = K_{t(e)} \cdot \dot{V}^2$) [Rodarte and Rehder, 1986]. The total pressure drop across the airways is the sum of all series pressure differences.

$$\Sigma P = \Sigma K_L \cdot \dot{V} + \Sigma K_t \cdot \dot{V}^{1.75} + \Sigma K_{t(e)} \cdot \dot{V}^2 \quad (6)$$

ΣP is the sum of all pressure losses, each of which is a specific function of $\dot{V}$. A simplified form of the above equation is used by most physiologists and is known as Rohrer's equation [Slonim and Hamilton, 1981]:

$$P = K_1 \cdot \dot{V} + K_2 \cdot \dot{V}^2 \quad (7)$$

where K_1 is equivalent to ΣK_L and K_2 is equivalent to $\Sigma K_{t(e)}$ and describe the relative contributions of laminar and turbulent airflow to mechanical energy losses, respectively.

The relationship between the P and $\dot{V}$ is dynamic resistance ($R = P/\dot{V}$). The work done ($W = P \times \Delta V$) to overcome flow resistance varies with the square of $\dot{V}$ during laminar conditions and its third power during turbulent flow. During exercise the oxygen cost of breathing at higher flow rates becomes greater as mechanical energy losses become greater due to turbulent airflow. As the viscosity of 21% O_2 in He is 1.1 times, and the density 0.34 times that of air, the critical velocity (for turbulent flow) must be approximately three times that in air [Murphy *et al*, 1969]. Flow in the airways is laminar at rest and becomes turbulent early in air-breathing exercise (still laminar with He-O_2 breathing). As ventilation increases with exercise, flow becomes turbulent with both gases. He-O_2 mixtures effect resistive unloading by reducing the resistance that is associated with turbulent flow during moderate or heavy exercise, for example.

3.3.1.1 The effects of breathing He-O_2 mixtures during exercise

Helium is an inert gas sometimes substituted for N_2 as a carrier gas in

breathing mixtures. He-O_2 mixtures are commonly used in research, diagnostic testing and hyperbaric applications. Their applications derive from their physical properties: low density, high kinematic viscosity (viscosity/density), high velocity of sound transmission and high thermal conductivity [Gilman *et al*, 1985]. The effect of He-O_2 breathing at sea-level on exercise and ventilation have been studied by many researchers. He-O_2 breathing has been found to increase [Fagraeus, 1974], decrease [Murphy *et al*, 1969] or have no effect on [Brice and Welch, 1983] oxygen uptake of exercising humans. There have been many studies that have examined the mechanical changes [Hussain *et al*, 1985., Nattie and Tenney, 1970., Zintel *et al*, 1990], chemical changes [Brice and Welch 1983., Ward *et al*, 1982] or exercise performance [Fagraeus, 1974., Spitler *et al*, 1974] while breathing He-O_2 mixtures. This section reviews some of the information available on the effects of He-O_2 breathing on ventilation and exercise performance.

Initial studies employing He-O_2 mixtures to unload the respiratory muscles, found the effects opposite to that of loading experiments [Nattie and Tenney, 1970]. Compared to air-breathing values, there was an increase in $\dot{V}E$ and f. A significant fall in $PACO_2$ was also observed. Mean inspiratory and expiratory flows increased, and a 33% increase in maximum voluntary ventilation was observed. Other studies that followed yielded similar results [Hussain *et al*, 1985, Ward *et al*, 1982]. The ventilatory effects were more pronounced when exercise was at 90% of AT[1] than at 50% [Ward *et al*, 1982]. It has been suggested that the subjects had to be

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1 AT, the anaerobic threshold represents the highest oxygen uptake that may be attained without elevation of arterial lactate concentration.

exercising at 70-85% of their peak $\dot{V}O_2$ to elicit a significant response [Spitler *et al*, 1980]. In a recent study [Zintel *et al*, 1990] intrapleural pressures were reported to be less negative with He-O_2 breathing during constant work heavy exercise, compared to air breathing values. This indicated that there was a fall in Pmus in spite of the increase in $\dot{V}E$. The work done by the respiratory muscles during He-O_2 breathing was considered to be reduced because of the lower intra-pleural pressures required for the increased ventilatory output.

The difference between humoral *vs* neuromechanical control of exercise ventilation has been highlighted by some authors [Hussain *et al*, 1985]. With the turbulent flows associated with exercise, He-O_2 mixtures allow higher flows for a given pressure. Under the AT, He-O_2 breathing induced a hyperventilatory response and hypocapnia. The ventilatory response was exaggerated with the addition of CO_2 to the breathing mixture. This seemed to indicate that preservation of blood-gas homoeostasis was dependent not only on humoral factors but also on the mechanical constraints (turbulent airflow) [Ward *et al*, 1982]. Above the AT however, other factors including rising body temperature, catecholamines and acid-base compensation tended to modulate the ventilatory response. All the above evidence suggest that the mechanical impedance presented by the normal time-constant of the healthy lung may be essential to the preservation of normocapnia in air breathing exercise [Dempsey *et al*, 1982]. It follows that both the metabolic demands of heavy exercise and the mechanical constraints of the respiratory pump have a role in modulating the ventilatory response to heavy exercise.

3.3.2 Mechanical assistance devices

In disease states (altered resistance and/or compliance) or under experimental conditions (resistive loading) the importance of mechanical factors in the control of exercise ventilation becomes evident. The sustained hyperventilatory response observed with breathing low-density gas mixtures at high work rates and the further increase in $\dot{V}E$ that was possible with the added CO_2 stimulation [Ward *et al*, 1982] suggests that the ventilatory response of exercise was constrained by turbulent airflow in the airways. However, neither the hypocapnia that resulted nor the diminished turbulence with He-O_2 breathing seemed to feed back to keep ventilation near control values. The reasons for this are not yet clear. The degree of resistive unload produced with He-O_2 breathing is limited and quite variable. Because the fall in turbulence is greatly dependent on airway geometry and flow rate, the effect is not uniform along the bronchial tree. The high kinematic viscosity of helium can reduce air flow in the peripheral small airways, where the pressure drop is predominantly due to viscous forces. Furthermore it is not possible to selectively unload one part of the respiratory cycle (I or E), using He-O_2 mixtures. So a different approach was needed to study the role of respiratory mechanical factors in the control of exercise ventilation in normal humans.

In the following sections, an overview of conventional pressure assisted ventilation is presented, followed by a detailed description of two different approaches to investigate the ventilatory responses to resistive pressure assist. In contrast to altering the resistance due to turbulent airflow, the pressure required to cause these flows is modified. Pressure assists are applied using modified ventilators

which directly alter the extrathoracic pressure gradient or intrapulmonary pressure.

3.3.2.1 Conventional assisted Ventilation

Pressure assisted ventilation has been used as a standard form of life support for many years. Ventilators, which are pressure assistance devices, are of two basic types which generate either a negative extrathoracic or a positive intrapulmonary pressure on inspiration. Normally the pressure difference required to move air into the lungs is produced by the chest expansion caused by inspiratory muscle contraction. Exhalation follows passively. Mechanical assistance sustains ventilation by generating the pressures required for inspiration. Negative extrathoracic pressures can be used to move the chest wall and abdomen outward causing a pressure gradient for inspiratory air flow. The *iron lung* and the *cuirass* (chest cage) type of ventilators fall into this category.

As well as providing the pressures required for air flow, these ventilators have a cycling mechanism to mimic the normal ventilatory patterns. These devices are classified on the basis of how inspiration is initiated; an assistor (subject triggered) or a controller (time triggered). Ventilators are further classified on the basis of how inspiration is terminated; pressure limited (when inspiration is terminated on reaching a preset airway pressure), volume limited (when a preset volume is delivered during inspiration), time limited (fixed T_I) or flow limited (termination of inspiration based on reaching a critical $\dot{V}$).

Although the above assistance devices are useful in a variety of clinical settings, they are limited in their applications to the assessment of respiratory-mechanical factors in normal healthy humans. The cycling of commercial ventilators

in synchrony with the subject's intrinsic rhythm is problematic. While initiation of inspiration is facilitated by the use of triggering mechanisms, the termination of the assist based on a preset volume, pressure or time may not necessarily coincide with the subject's natural phase transition from I to E [McPherson, 1977]. The ventilatory responses to such devices is bound to be contaminated with the voluntary responses of the subject as well as mechanoreceptor reflexes from the chest wall and lungs.

3.3.2.2 External (body surface) Unloading

This modification of a tank type respirator was presented by Harries and Tyler in 1964. The subject sat in and was enclosed by an air-tight tank (from the neck down) and the tank pressure was controlled such that it was proportional to the chest excursions of the subject. This was essentially a patient controlled servo-respirator (figure 3.1) capable of applying negative extrathoracic pressures proportional to

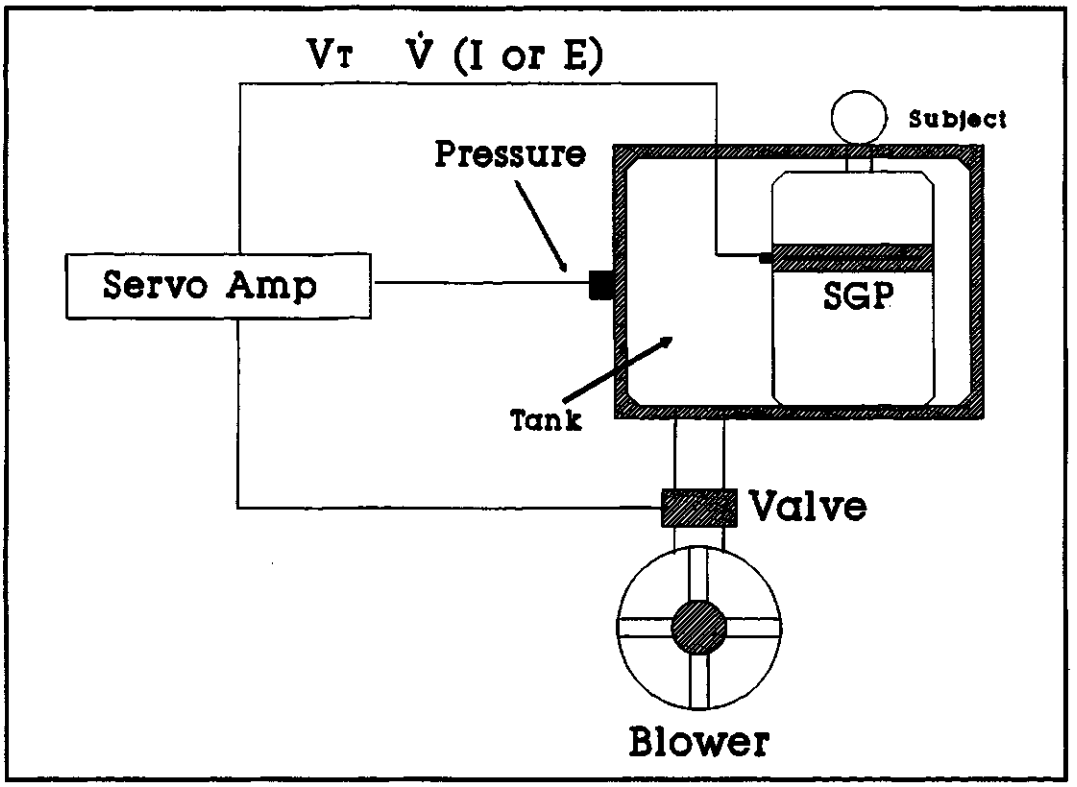

Figure 3.1: Patient-controlled Servorespirator

either V_T, $\dot{V}$ (I or E) or a combination of all three. A strain gauge pneumograph (SGP) provided an electrical signal proportional to the circumference of the patient's chest and this was calibrated for volume. This signal yielded by continuous analog differentiation, one component each for inspiratory and expiratory flow. Each of these signals had an independent gain control and could be used individually or in combination, as the input to the servo-amplifier which controlled the sleeve valve opening between the blower and the tank. A pressure transducer mounted in the tank monitored intra-tank (negative) pressure. It was therefore possible to apply negative extrathoracic pressures proportional to V_T (elastic assist) and/or $\dot{V}$ (I and/or E, resistive assist). In most of the patients with emphysema studied using this servo-respirator, there was a significant increase in $\dot{V}_E$. A significant fall in $\dot{V}O_2$ was recorded without any increase in ventilatory output in a few subjects, suggesting that the work of breathing might have been reduced. Inspiratory resistive assist produced a significant change in $\dot{V}_E$ whereas expiratory resistive assist alone did not. This design was a significant improvement over extrathoracic negative pressure ventilators, as the external pressure remained in synchrony with the subjects intrinsic breathing pattern and thus substantially reduced mechanical distortions. The device was however limited in its applications because of its size and construction. In addition it could not be set up for exercise studies because of its slow response.

3.3.2.3 Inspiratory Resistive assistance device

More recently [Poon and Ward, 1986] commercially available ventilators have been modified to apply airway pressures proportional to an external command signal. Figure 3.2 describes schematically one such device which applied a positive mouth

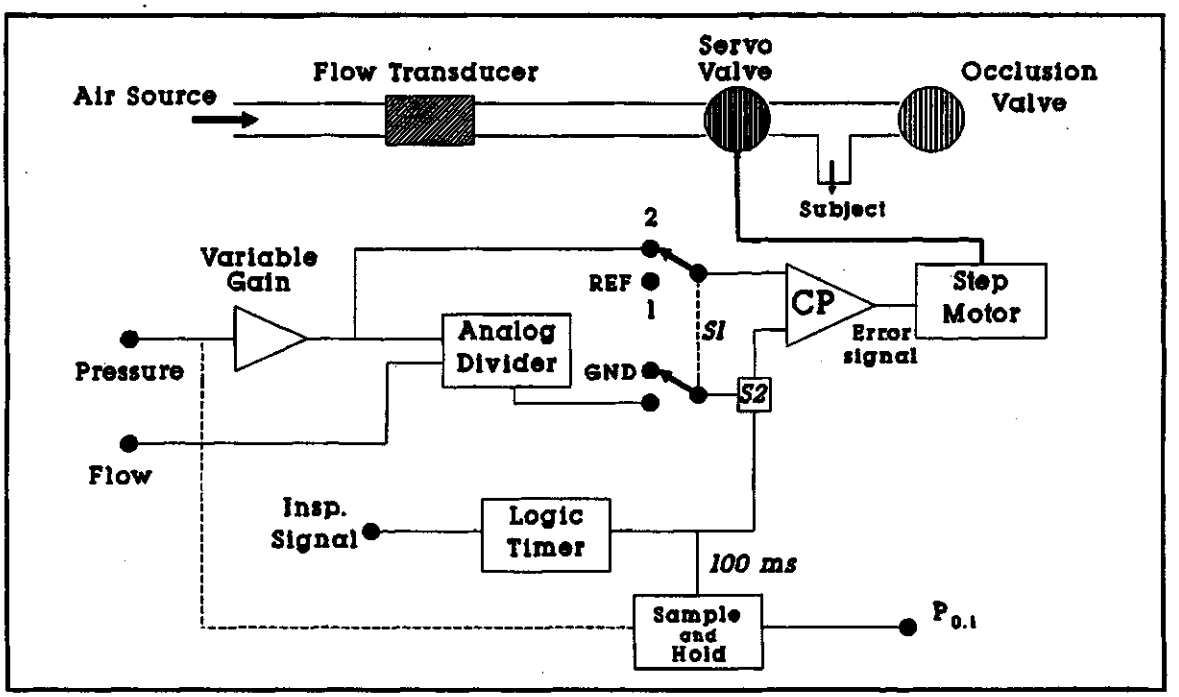

Figure 3.2: Inspiratory resistive assistance device.

pressure proportional to inspiratory flow (inspiratory resistive assist).

The basic unit was a commercially available servo-ventilator (Siemens-Elema #900B). It was designed to generate a sinusoidal or a square wave profile of inspiratory airflow, using a servo-mechanism which continuously compares the airflow achieved to the airflow desired. The resulting error signal was used to drive a step-motor that controls flow by altering the patency of a servo-valve. The inputs to the error-calculating stage (Comparator, CP) were modified such that airway resistance ($Pm/\dot{V}(I)$) was compared to a desired assist level (REF). The resulting error signal was used to drive the step-motor. An electronically controlled pneumatic occlusion valve on the expiratory side of the breathing valve remained closed during inspiration.

$P_{0.1}$ is the mouth pressure developed after the start of spontaneous inspiration, obtained during a brief occlusion at the mouth (100 - 150 ms). This represents the

total pressure across the respiratory system as a result of inspiratory muscle contraction at this time [Milic-Emili *et al*, 1981]. In order to monitor breath-by-breath changes in $P_{0.1}$, a timing mechanism was included in the design. The inspiration signal was the input to a logic circuit and timer such that it kept the electronic switch (S2) open throughout expiration and for 120 ms into the start of inspiration. $P_{0.1}$ was the output of the sample and hold circuit. The system operated in the assist mode when the switch S1 (manually operated DPDT) was in position 1, when the inputs to the comparator were $Pm/\dot{V}(I)$ and REF. In the control mode the switch S1 was in position 2 and referenced the pressure signal to ground (GND) keeping mouth pressure zero throughout inspiration. By controlling the REF level, two types of assists were used: low level assist when $Pm/\dot{V}(I)$ was controlled to approximate an unload (R) of 1.5 $cmH_2O \cdot l^{-1} \cdot s$ and a high level assist when R = 3.0 $cmH_2O \cdot l^{-1} \cdot s$. These levels corresponded approximately to 50% and 100% of normal inspiratory resistance of the subjects.

The device was evaluated during moderate levels of exercise in both the control and the assist mode in five subjects. Both the low and the high levels of assists were used. The control and the assist modes were applied in a randomised order for each subject and for each workload. The authors [Poon and Ward, 1986] demonstrated that Pm was elevated throughout inspiration, continuously tracking flow. The instantaneous $Pm/\dot{V}(I)$ ratio was thus held constant except for overshoots or undershoots (± 20%), mostly due to transients around flow zero-crossings as well as due to gas compression in the tubing. The desired $Pm/\dot{V}(I)$ ratio was reached typically 50 ms after inspiratory onset. The rise time was dependent on the level of

assistance as well as the rate of rise of the flow signal. The response of the entire system was generally satisfactory, except at the highest airflows achieved (6 $l \cdot s^{-1}$) along with the high level of assist (R = 3.0 $cmH_2O \cdot l^{-1} \cdot s$), when the pressure tended to fall due to the abrupt emptying of the air source (bellows).

On application of the assist, immediate ventilatory changes were observed. There was an immediate augmentation of $\dot{V}(I)$ and a significant fall in TI. An initial significant increase (45%) in $\dot{V}E$ and a fall in $PETCO_2$ was observed. $P_{0.1}$ did not show any change initially. Ten to fifteen seconds after the application of the assist, $P_{0.1}$ fell gradually and stabilised at a level that was ~50% of the control value. $\dot{V}E$ also fell and $PETCO_2$ increased gradually to control values. The reverse pattern of responses was seen after the withdrawal of assist.

This technique of inspiratory resistive assist applied during both rest and moderate exercise by this device differs from density-dependent unloading, where turbulent air flow is necessary before unloading is possible. Using this servo-ventilator it was also possible to impose controlled levels of inspiratory assist on a breath by breath basis. The authors [Poon and Ward, 1986] envisaged that this assisted ventilation technique could have a variety of clinical applications in addition to its demonstrated use in physiological research. The improved synchrony of the applied pressure waveform with the inspiratory flow signal could be very useful in the design of an assistor type of ventilator. It could allow the subject to set the rate and depth of breathing, i.e., for a given VT, the pressure assist reduces the resistive work of the respiratory muscles.

3.4 Summary

Alteration of the mechanical load on the respiratory system has been a useful technique in respiratory physiological investigations Application of the load either at rest or during exercise has helped in the understanding of the intrinsic mechanical properties of the respiratory pump and the interactions between the mechanical and chemical influences on exercise ventilation. The simulation of specific mechanical derangements occurring with lung (and/or chest wall) disease was done by applying the appropriate (elastic or resistive) load. Resistive unloading of the respiratory system was possible with the help of low-density gas mixtures and pressure assist devices. The principles involved, and the results of such unloading have been briefly reviewed. He-O_2 breathing during exercise induced a pronounced increase in minute ventilation along with hypocapnia. This has raised more questions about the role of mechanical and chemical factors on exercise ventilation. Although resistive unloading occurs both in the case of He-O_2 and flow proportional pressure assist, there are essential differences in the ventilatory response between the two techniques.

4. THE LOADING/UNLOADING DEVICE

4.1 Introduction

Full wave (I and E) resistive unloading of the respiratory muscles at rest and during exercise has become possible with the recent development of a feedback-controlled loading/unloading device [Younes *et al*, 1987]. This device is able to generate pressures in response to various command signals and is an improvement over conventional ventilators. Electronic controls permit a choice between loading or unloading, the type (elastic, resistive) of load/unload and control over the magnitude, pattern, duration and the timing of application (I and/or E), of the altered load/unload. It is also possible to selectively unload one half of the breathing cycle (I or E) at rest, using this device. This is in contrast with He-O_2 unloading which, effective only with turbulent flows (e.g. exercise), unloads throughout the breathing cycle. For a complete description of the design, evaluation and the uses of this device in respiratory research, the reader is referred to the original article [Younes *et al*, 1987].

The objective of this thesis was to set up a prototype of this device for full wave resistive respiratory muscle unloading during heavy exercise. Initially, in this chapter, a brief overview of the design and principles of operation of the original device (figure 4.1) is presented. In addition to introducing the reader to the operation of this device it emphasizes the extent of modifications that were essential to achieve the thesis objectives. The device and its accessories were assembled, tested and set up for pilot unloading studies on human subjects. The author received

assistance and guidance from the technical staff in the laboratory in these tasks. A number of problems were revealed as a result of conducting the pilot studies and were corrected. A detailed description of the initial assembly, testing and the results of the pilot studies is provided in the following sections. The modifications that were necessary and the subsequent evaluation of the unloading device in FWUL during heavy exercise are described in detail. The device and the modifications were then successfully evaluated for use in a study in which proportional FWUL were applied in normal healthy human subjects performing prolonged exercise to exhaustion.

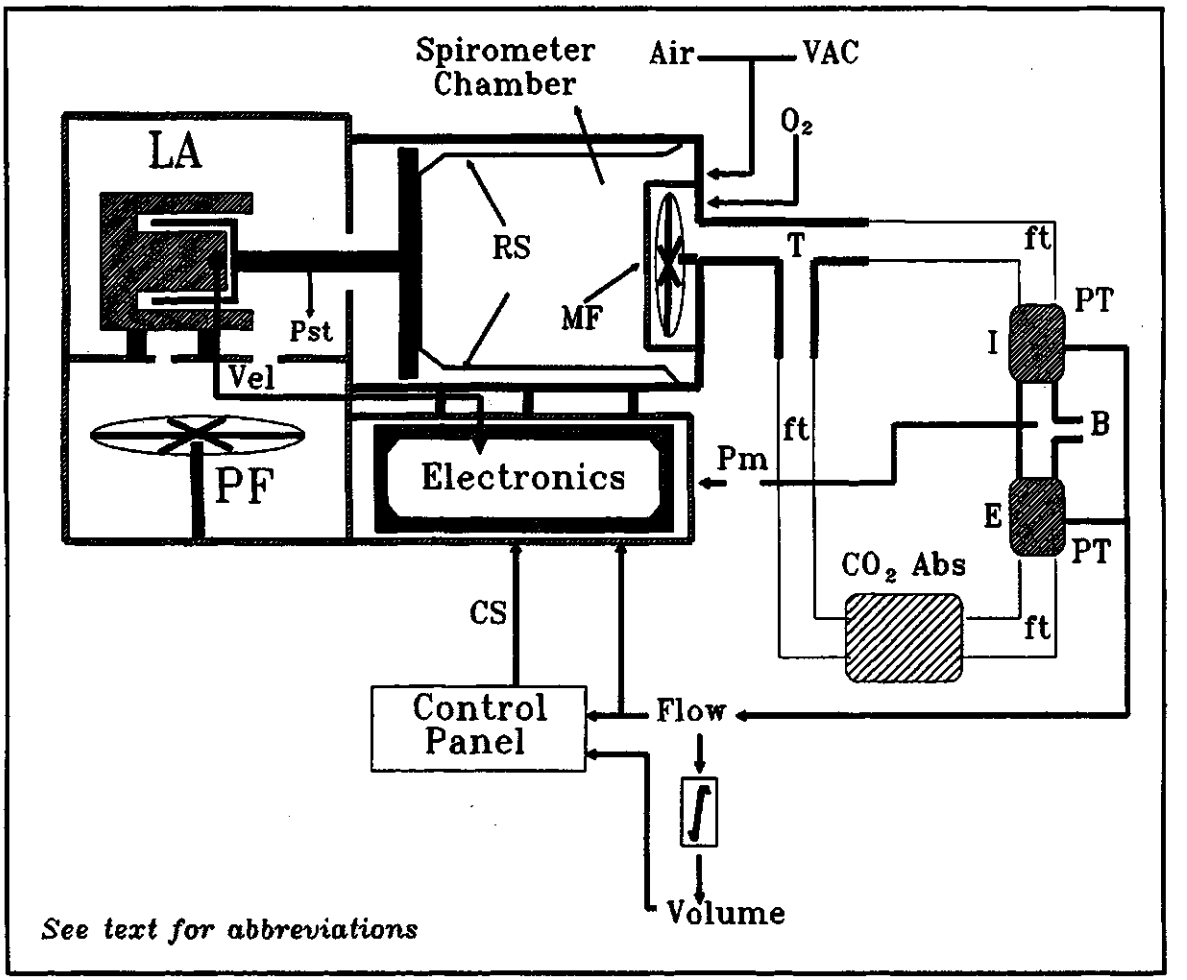

Figure 4.1: Loading/Unloading device - Original design [Younes *et al*, 1987]

4.2 Apparatus design [Younes *et al*, 1987]

4.2.1 Pressure generating unit

A rolling seal (RS) spirometer (OHIO, model 822) driven by a linear actuator (LA) was used to generate pressures. The spirometer with its low static and frictional resistance was stable because of its stainless steel cylinder and reinforced aluminium piston (Pst). The front opening of the spirometer was sealed with a detachable plate with a 1½" port common to both inspiratory and expiratory tubing. There were three additional ports for gas inlets. A potentiometer mounted on the spirometer housing, monitored piston position. The linear actuator (Burroughs, disk drive system, model B94-944) was selected based on the following considerations. It had a continuous linear motion (as opposed to stepwise). The cross-sectional area of the spirometer was 660 cm^2 such that the full extension of the bobbin and shaft (9 cm) displaced ~6 l. The actuator was able to match the high flow velocity and volume accelerations (e.g. linear velocity of 10 $cm \cdot s^{-1}$ for a $\dot{V}$ of 6.6 $l \cdot s^{-1}$ and linear acceleration of 150 $cm \cdot s^{-2}$ for a $\dot{V}$ of 100 $l \cdot s^{-2}$) usually generated by subjects at maximal exercise. The actuator was also able to generate sufficient pressures. Given a piston area of 660 cm^2, the force required to generate a pressure of 1 cmH_2O was 0.66 Kg. The maximum pressures that developed in the spirometer chamber ranged ± 20 cmH_2O. The actuator was affixed carefully on a platform (figure 4.1) and its shaft and the spirometer piston were aligned in such a way that the bobbin, fully extended (9.5 cm) displaced 6.3 l. This left room to mount a mixing fan (MF, muffin fan, EG+G Rotron) on the inner surface of the front plate of the spirometer. The actuator was cooled by a plenum fan (PF).

4.2.2 Plumbing and other connections

The limbs of a 'T' shaped piece of ABS tubing (1½") connected to the front face of the spirometer (figure 4.1) formed the inspiratory and expiratory arms of the closed breathing circuit. Three smaller ports were used for 100% O_2, compressed air (Air) and vacuum pump (VAC) connections. All other plumbing was done with flexible 1½" tubing (ft) connecting the spirometer to the inspiratory and expiratory arms of the breathing (Rudolph) valve (B). The expiratory line incorporated a CO_2 absorber (CO_2 abs) for complete CO_2 absorption. Inspiratory and expiratory flows were measured separately with pneumotachometers (PT) on either side of the breathing valve. Because the apparatus was a closed system, O_2 concentration could be set at any desired level by controlling O_2 flow and then maintained within the range desired (21 - 23%). The subject breathed through a short mouthpiece (with a saliva trap) attached to the breathing valve. Breath-by-breath Pm and end-tidal gases were monitored at the mouth.

4.2.2 Electronics

The loading-unloading device operated in such a way that the linear actuator generated a positive or negative pressure matching a command signal (CS), such that the error (CS - Pm) was minimised (Figure 4.2). The command signal (e.g. $\dot{V}$ or V) determined the type (elastic, resistive) of load/unload. The nature, timing and magnitude of the command signal were adjusted from a control panel. The DRIVE signal controlling the linear actuator was the output of the pre-amp (x10) whose input is the amplified (x1.3) error signal. The output of the pre-amp was fed back to its input (negative feedback).

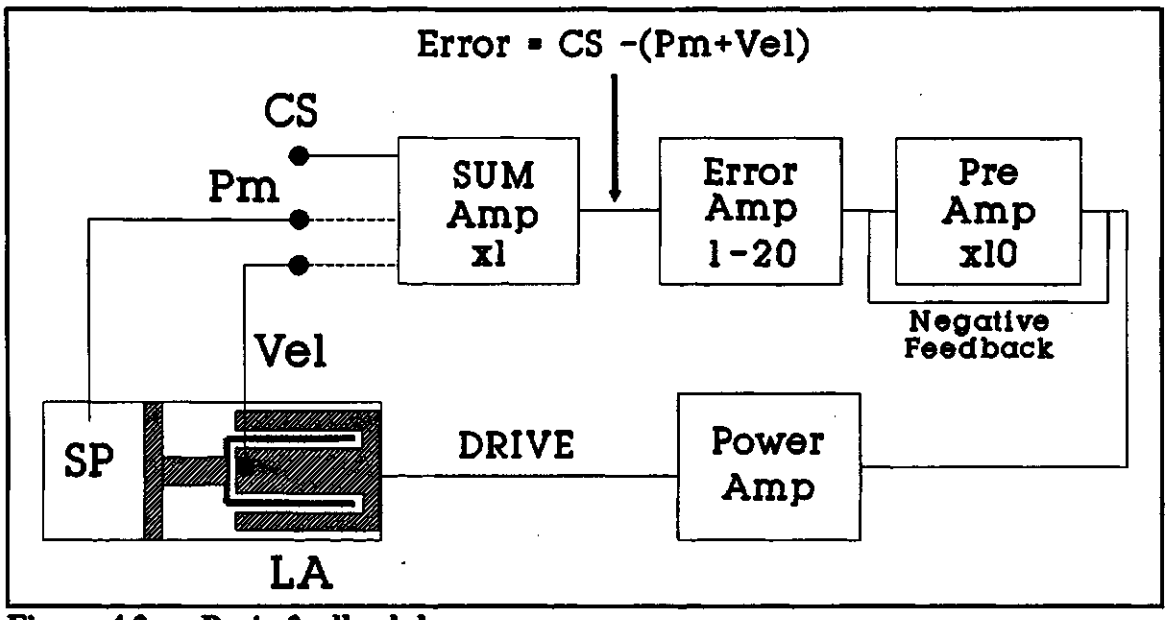

Figure 4.2: Basic feedback loop.

An error signal resulted when the mouth pressure (Pm) and velocity (Vel) signal from a transducer on the linear actuator (both opposite in polarity to command) are subtracted from the command signal. This error decreased as Pm approached the amplitude and shape of the command signal. The site from which pressure feedback was derived (breathing valve or the spirometer chamber) determined the site at which pressure was controlled. Utilizing spirometer pressure as feedback ensured a better tracking of the command signal by the pressure signal (required less velocity feedback), but did not compensate for the resistance of the plumbing between the spirometer and the breathing valve. Generally Pm was used as feedback, as was the case in this study. Both the command signal and Pm were filtered before the adder, to reduce high-frequency noise in these signals which tended to trigger oscillations. The command signal was filtered at 10 Hz when it was noisy (CS $\propto \dot{V}$) or at 50 Hz (CS $\propto$ V, less noisy). Pm was filtered at 50 Hz.

The system had an inherent tendency to oscillate because of pressure feedback. The compliance and the resistance of the system (including tubing) caused mechanical delays resulting in Pm being slightly out of synchrony with the command signal thus making the system unstable. In order to reduce the chances of oscillation the signal from a velocity transducer on the linear actuator was added to the feedback (figure 4.2). This "raw" velocity signal was related to: (1) the air flow between the subject and the spirometer ($\propto$ to $\dot{V}$); (2) Compression and decompression of the gas in the system ($\propto$ to spirometer pressure). Only the latter component related to the pressure changes in the system was used for feedback. The component related to the flow signal was subtracted from the raw velocity signal using a summing amplifier (A, figure 4.3): the gain on the flow signal was adjusted

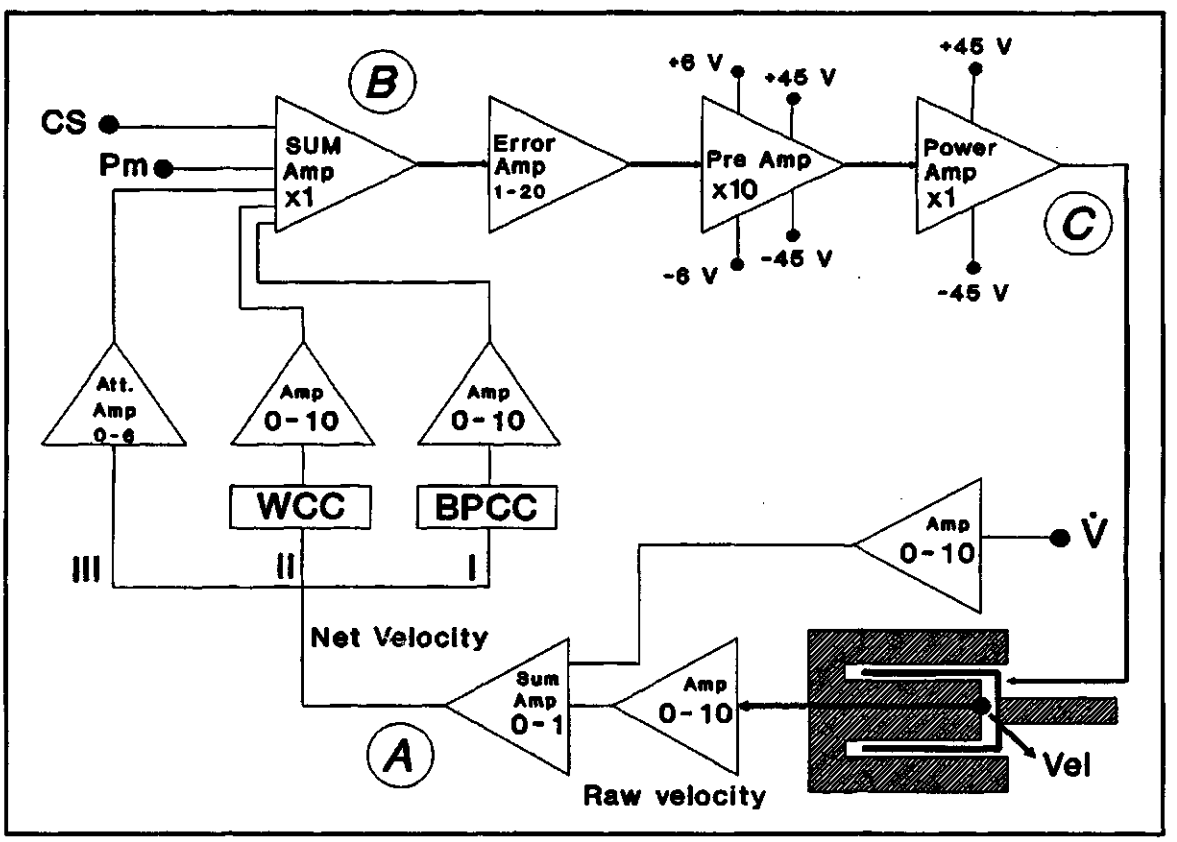

Figure 4.3: Chassis Electronics

so that it cancelled the raw velocity signal when the spirometer was ventilated passively with a respirator (P = 0). With loading or unloading the Sum amp output (*A*, figure 4.3) reflected that component of the velocity signal related only to the pressure changes in the system. This "Net" velocity signal was used as feedback.

Initial testing of the design revealed that the addition of net velocity feedback to eliminate oscillations under all conditions made the system response very slow. The origin of oscillations was studied and a detailed velocity feedback system was designed. Oscillations were generated when the system pressure approached the desired pressure. Mechanical delays caused pressure overshoots and undershoots, thus causing oscillations of gradually increasing amplitude until the pressure reached the possible maximum (± 20 cmH_2O) at a frequency of 10 - 20 Hz. At the point of initiation of oscillation the rate of pressure change (hence the velocity signal) was found to be small. By increasing the gain of the net velocity signal when it was small, initiation of oscillations was averted without having to increase the gain over the entire velocity feedback signal range. This system of maximising the feedback over the small signal range is described below.

4.2.2.1 Net Velocity feedback

The net velocity signal was divided through three pathways (I, II and III, figure 4.3). One arm of the net velocity signal (**I**) was the input to a bi-directional peak clipping circuit (BPCC), which clipped the signal below and above a DC offset. The resultant signal (± DC offset) was then amplified to increase feedback over that range. This part of the feedback was in operation when the rate of pressure change in the system (hence net velocity) is high, as occurring with high flow rates of heavy

exercise. The second arm (II) of the net velocity signal was passed through a window clipping circuit (WCC, figure 4.3). This circuit passed that portion of the net-velocity signal that is above and below a DC offset level and was designed to avert oscillations in case the other feedback failed. The offset level set for the WCC was greater than the normal range of the net velocity signal (± 1.5 V) associated with the physiological range of the command signal. The third arm (III) of the net velocity signal was passed directly through an attenuator/amplifier (Att.Amp, figure 4.3). The 10-turn potentiometer control for this limb was mounted (for easy access) on the spirometer chassis and was used to increase or decrease net velocity during an experiment.

4.2.3 Control Panel Electronics

The nature, timing and the magnitude of the command signal were adjustable using the control panel amplifiers, attenuators, inverters and rectifiers. An ON/OFF switch was used to ground the command signal (load/no-load). Figure 4.4 lists

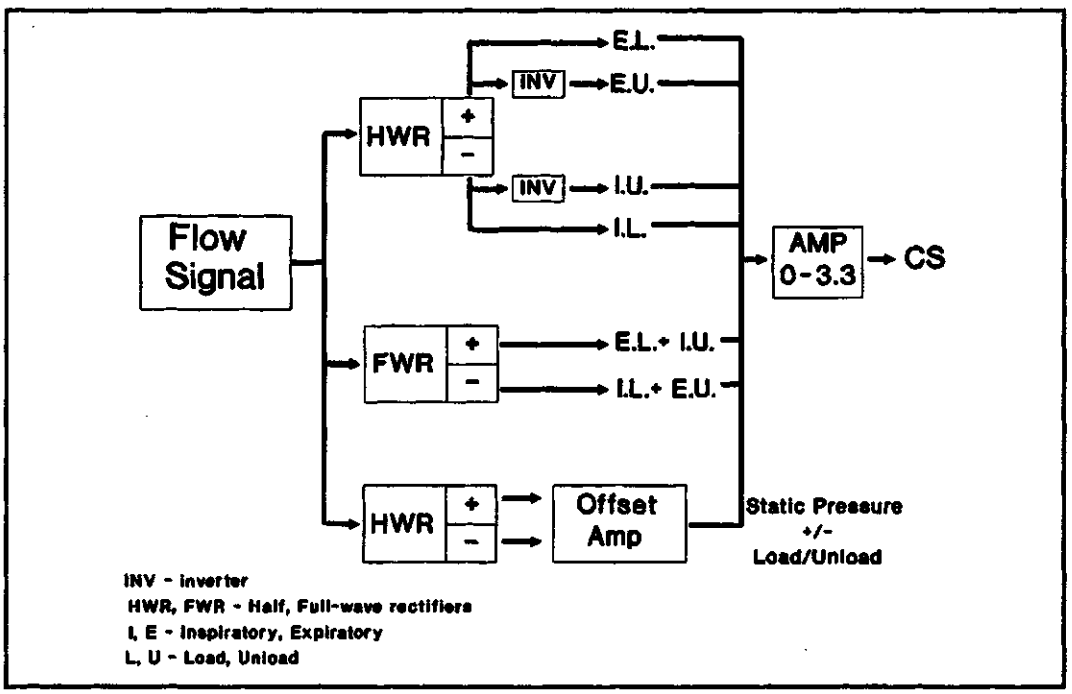

Figure 4.4: Half-wave loading/unloading - CS configurations

schematically the possible command signal configurations for half-wave (I or E) resistive loading/unloading. For resistive loads/unloads the output of the $\dot{V}$ attenuator was the input to the appropriate rectifier and inverter, to select the phase (I or E) and polarity (load/unload). An inspiratory resistive load for example, could be applied when the negative half-wave rectifier output was used (inspiratory $\dot{V}$ was negative). A non-inverting amplifier (Amp 0 - 3.3, figure 4.4) was used to control the gain of the command signal before it was added to Pm and Vel signal (*B*, figure 4.3).

The command signal configurations necessary for full-wave (I and E) loading/unloading are illustrated in figure 4.5. Full wave resistive loading/unloading was effected when the input to the command signal amplifier was the direct/inverted

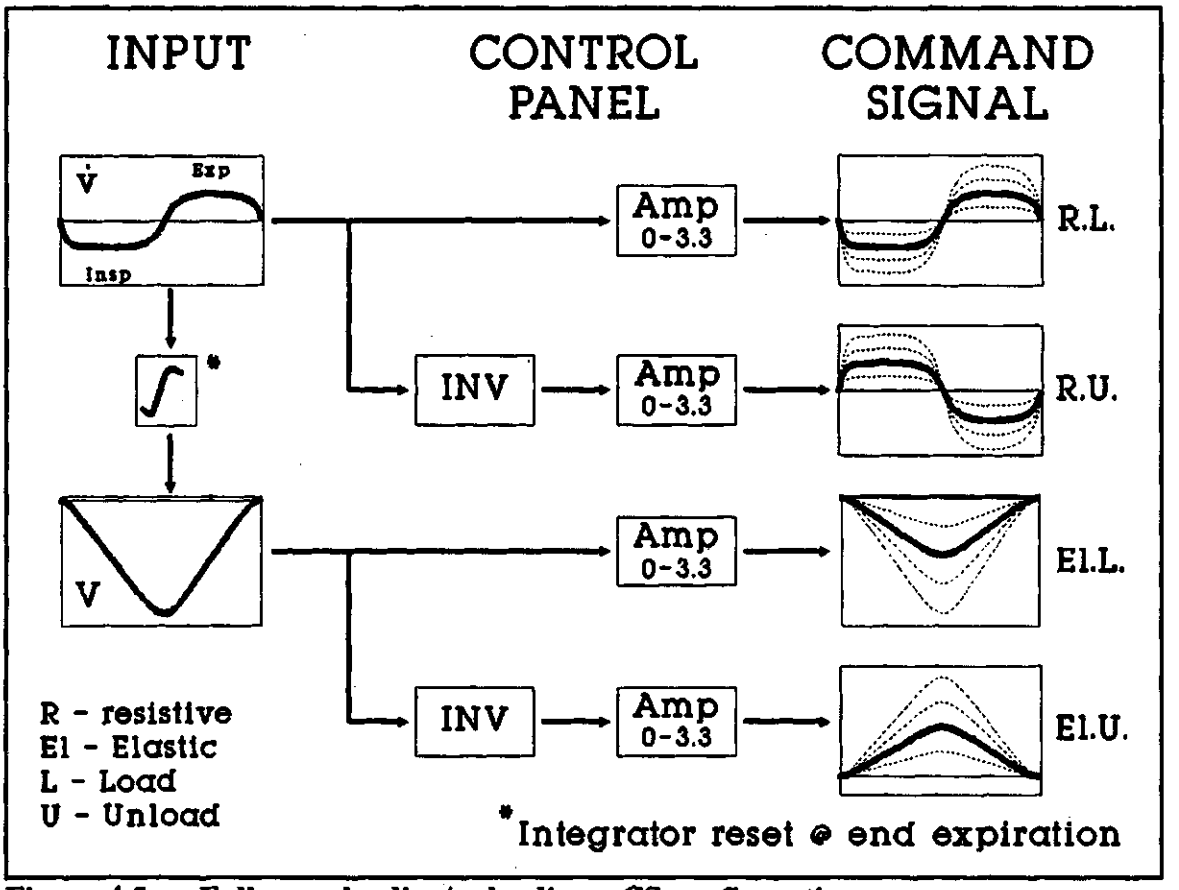

Figure 4.5: Full-wave loading/unloading - CS configurations

$\dot{V}$ signal. A 10-turn potentiometer allowed easy setting of the command signal amplifier gain (0-3.3). The degree of loading/unloading however was limited by the maximum pressure capacity of the system (± 20 cmH_2O). For full-wave elastic loads/unloads, the direct/inverted volume signal was used as command signal amp input. With elastic loading/unloading the output of the flow integrator was reset to zero at end expiration to prevent electrical drifts in the integrator causing proportional changes in end expiratory pressure.

It was possible to apply continuous positive or negative pressures, by dialling in an appropriate offset on the voltage source of the offset amplifier available on the control panel. The output of the offset amplifier could then be the input to the command signal amplifier (figure 4.4). Combined loads (e.g. inspiratory resistive load + continuous negative pressure) could be applied by using $\dot{V}$, V or an external signal as input to the offset amplifier. Pm could also be made to change in proportion to any external function (ramp, sinusoid, square wave), by using a command signal based on a function generator's output (after appropriate filtering, rectification etc.). The timing of load/unload application was controlled using the flow signal (to identify I and E) as a gating input to the function generator.

4.3 Initial prototype testing

This proposed study was conducted using a prototype of the loading/unloading device, described so far. The device and its accessories were assembled and were initially tested for an optimal pressure response to various command signals. In the following sections only the relevant details of evaluation of the unloading device for full-wave (I and E) resistive unloading (FWUL) are presented. Initially, FWUL was

applied to an animal ventilator. Then the unloading device was tested for its ability to unload human subjects at rest and during heavy exercise.

4.3.1 Response to square wave inputs

The stability of the unloading device was tested by its ability to match a square wave command signal. For this, the inspiratory and expiratory limbs of the spirometer inlet were occluded, and pressure feedback was obtained from the spirometer chamber. Two levels (2 V, 4.5V @ 20 - 30/min) of negative square wave inputs (from a function generator) were applied. Only the external net velocity feedback control was used to increase/reduce feedback, to test for the device's tendency to oscillate. Figure 4.6 shows the results from one such test. The linear actuator responded 15 ms (lag time) after the square wave onset and spirometer pressure rose exponentially to 90% of peak in ~70 ms (response time, 65 - 90 ms). The external net velocity feedback control was effective in preventing the onset of oscillations, but did not affect the lag and response times in the range used (0.1× -

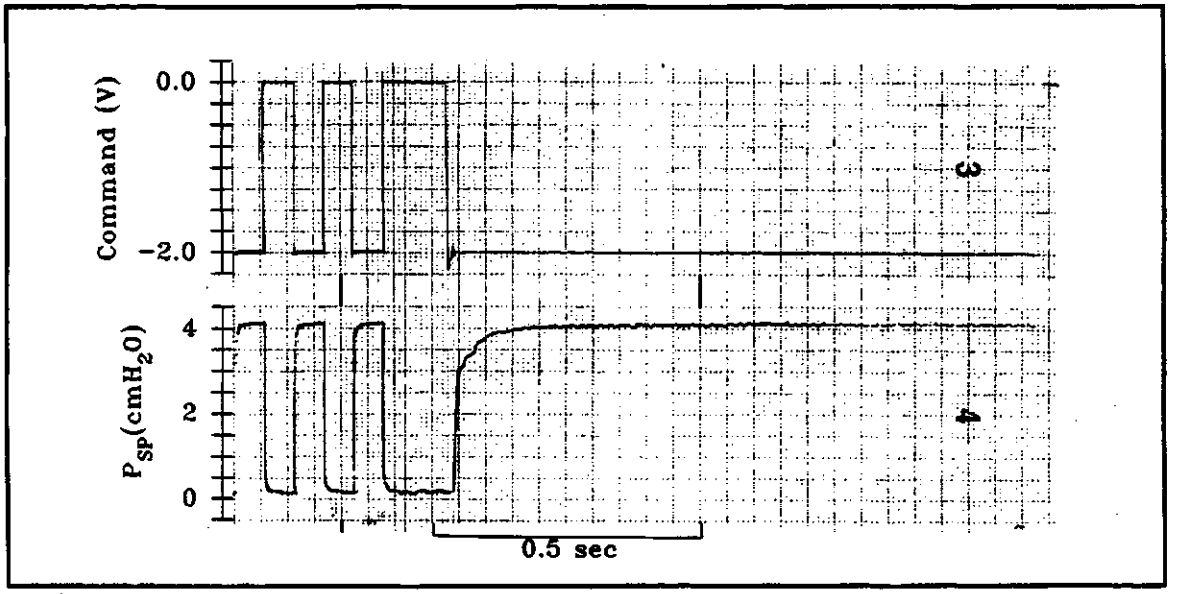

Figure 4.6: Pressure response to a square wave C.S

0.7×). Shorter response times were obtained with the - 4.5 V command signal input.

4.3.2 Animal ventilator studies

After establishing the stability of the unloading device in matching square wave inputs, FWUL was applied to an animal ventilator (Harvard Model 613, stroke volume 750 ml). As illustrated in figure 4.7, the unloading device was connected on the inspiratory side to a two way non-rebreathing valve (B, Hans-Rudolph Inc. #2700), and on the expiratory side to the outlet of the CO_2 absorber canister. The expiratory port of the breathing valve was connected to the CO_2 absorber inlet, thus completing the closed breathing circuit. All connections were made with 1½" flexible tubing and were leak free. The command signal was flow from the animal ventilator (AV). Inspiratory and expiratory flows were measured with separate pneumotachometers/transducers (Fleisch #3/Validyne MP45 ± 2cmH_2O) and were added electronically to provide flow throughout the ventilator cycle. Pm was obtained from a port in the breathing valve.

Results of animal ventilator unloading revealed that the overall response of

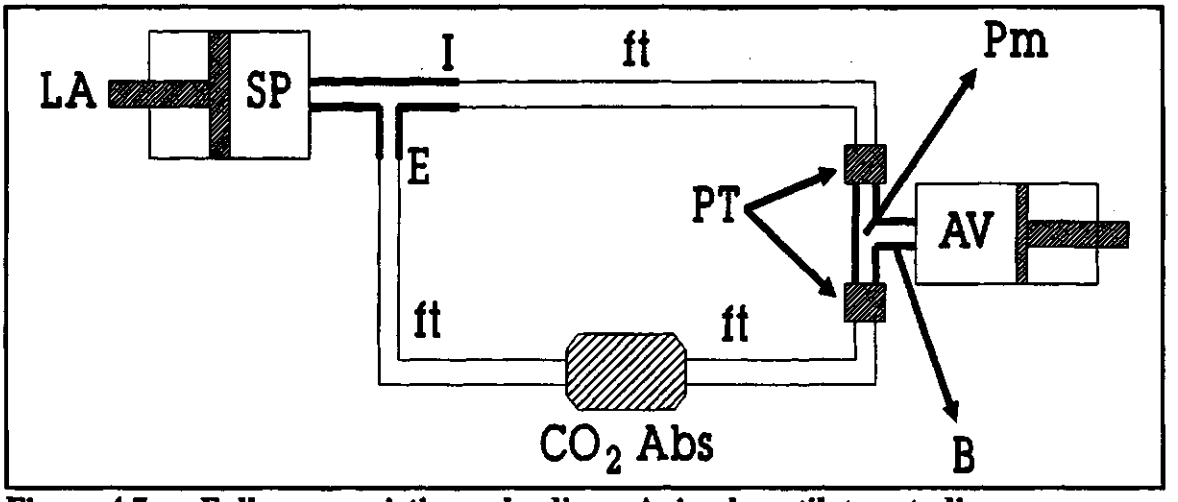

Figure 4.7: Full-wave resistive unloading - Animal ventilator studies

the unloading device was slow with very long lag times (I → E and E → I) between the sinusoidal flow (command) and the pressure signals. Reducing the external net velocity feedback did not reduce these lag times indicating that a net reduction in feedback was necessary to improve the response characteristics of the device. The unloading device was used in the same configuration as in figure 4.7. The animal ventilator provided flows (peak 1.5 $l \cdot s^{-1}$ @ 20-30 /min). The device was used in the control mode (CS = 0), when the system pressure changes are minimal. The gain on the raw velocity signal was reduced (by 30%) and the gain on the flow signal adjusted such that the output of the summing amplifier (*A*, Sum Amp 0-1, figure 4.3) was minimal. The output of the summing amplifier with unloading represented that component of the Vel signal related to the pressure changes in the system. The unloading device was then switched to the unload mode (CS ∝ $\dot{V}$). The results of animal ventilator FWUL are in table 4.1.

Table 4.1 Results of animal ventilator unloading

Flow ($l \cdot s^{-1}$)		Command (Volts)		Pressure (cmH_2O)		Unload ($cmH_2O \cdot l^{-1} \cdot s$)		Net velocity Feedback	Lag time (ms)	
I	E	I	E	I	E	I	E	(gain)	I → E	E → I
0.9	0.9	0.5	0.5	1.1	1.0	1.2	1.1	0.5	235	205
								1.5	280	195
		1.4	1.5	2.9	2.8	3.2	3.1	0.5	160	95
								1.5	170	110
1.7	1.8	1.0	0.9	2.1	1.9	1.3	1.1	0.5	200	115
								1.5	200	135
		2.7	2.8	5.2	6.0	3.2	3.3	0.5	80	80
								1.5	115	85

Two levels of flow inputs were used (0.9, 1.7 $l \cdot s^{-1}$, peak) and two levels of unloading (1.2, 3.2 $cmH_2O \cdot l^{-1} \cdot s$) were attempted. By reducing the amount of raw velocity feedback, a significant improvement in lag times was observed. The external net velocity feedback control was more effective in increasing/reducing the level of net velocity feedback and had an improved role in controlling oscillations and response characteristics of the system. The response of the system was better with the larger command signal (*cf.* square wave response). Typical waveforms ($\dot{V}$ and P) from this test are shown in figure 4.8. Inspiratory flow was negative. The pressure signal was positive throughout inspiration except for the first 55 ms (E → I lag time) when it was slightly negative. Similarly, pressure was negative during most of expiration with an I → E lag time of 100 ms. The longer lag at the I → E transition was probably due to the noise (animal ventilator piston vibrations) in the flow signal.

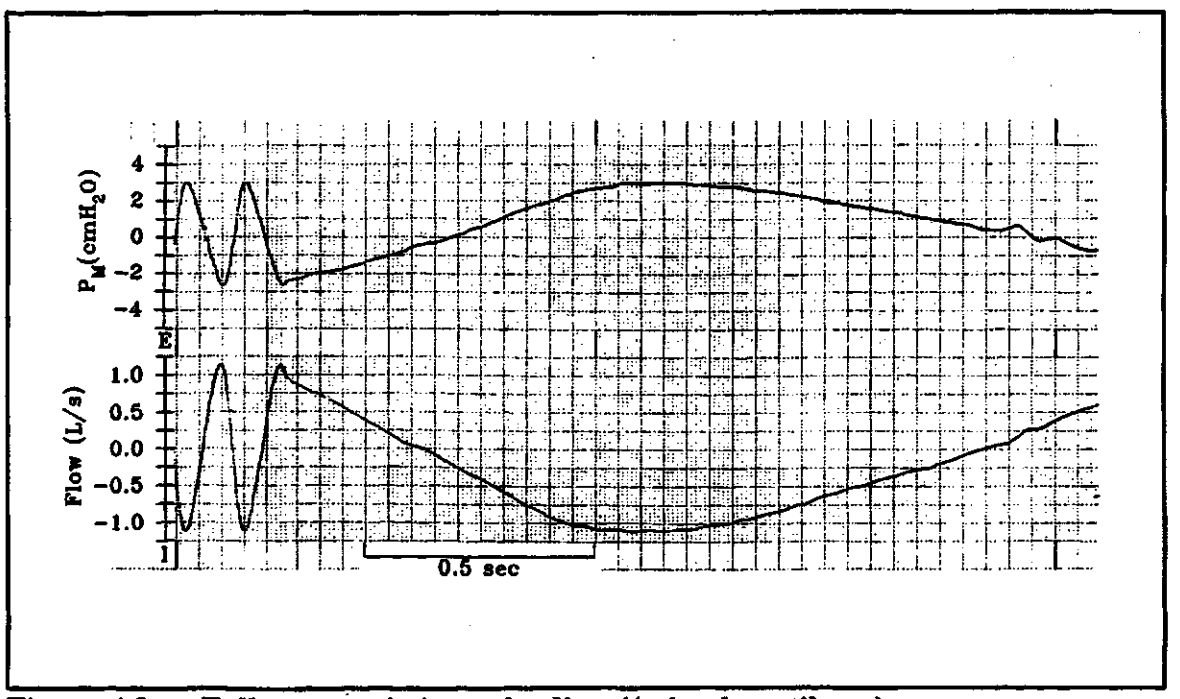

Figure 4.8: Full-wave resistive unloading (Animal ventilator)

4.3.3 Pilot studies

After testing the unloading device with resistive unloading at rest in normal human subjects, FWUL was applied in four male subjects (average age 25 yrs) performing constant load exercise to exhaustion on a bicycle ergometer (Godart #18070). The subjects were well motivated and gave informed consent. $\dot{V}O_2max$ was assessed using an incremental exercise protocol (50 watts for 1 minute with 25 watts increments every minute until exhaustion) on the bicycle ergometer. The body plethysmograph technique (Chapter 5) was used to measure Raw in these subjects. At least four days after the incremental tests, the subjects performed constant load exercise at a level that represented 85 - 90% of $\dot{V}O_2max$ (range 190 - 270 watts), on two days. The subjects breathed from the closed breathing system and unloading device on both days. Expired CO_2 was absorbed by self-indicating soda-lime. Inspiratory and expiratory flows were measured with separate pneumotachometers/transducers (Fleisch #3/Validyne MP45 $\pm$ 2cmH_2O) on either side of the breathing valve (Hans-Rudolph #2700). Pm feedback was obtained from the mouth piece. On one occasion the unloader was operated in the control mode (CS = 0, Pm = 0, figure 4.9), and on the other proportional resistive unloads (75% of the subjects' total resistance) were applied throughout exercise. With unloading, mouth pressure was positive during inspiration and negative during expiration (figure 4.10). The subjects exercised to exhaustion.

4.3.3.1 Results

Figure 4.9 shows the results from the control test in one subject. Data from three periods (at rest, 3 minutes into heavy exercise and at end exercise) during

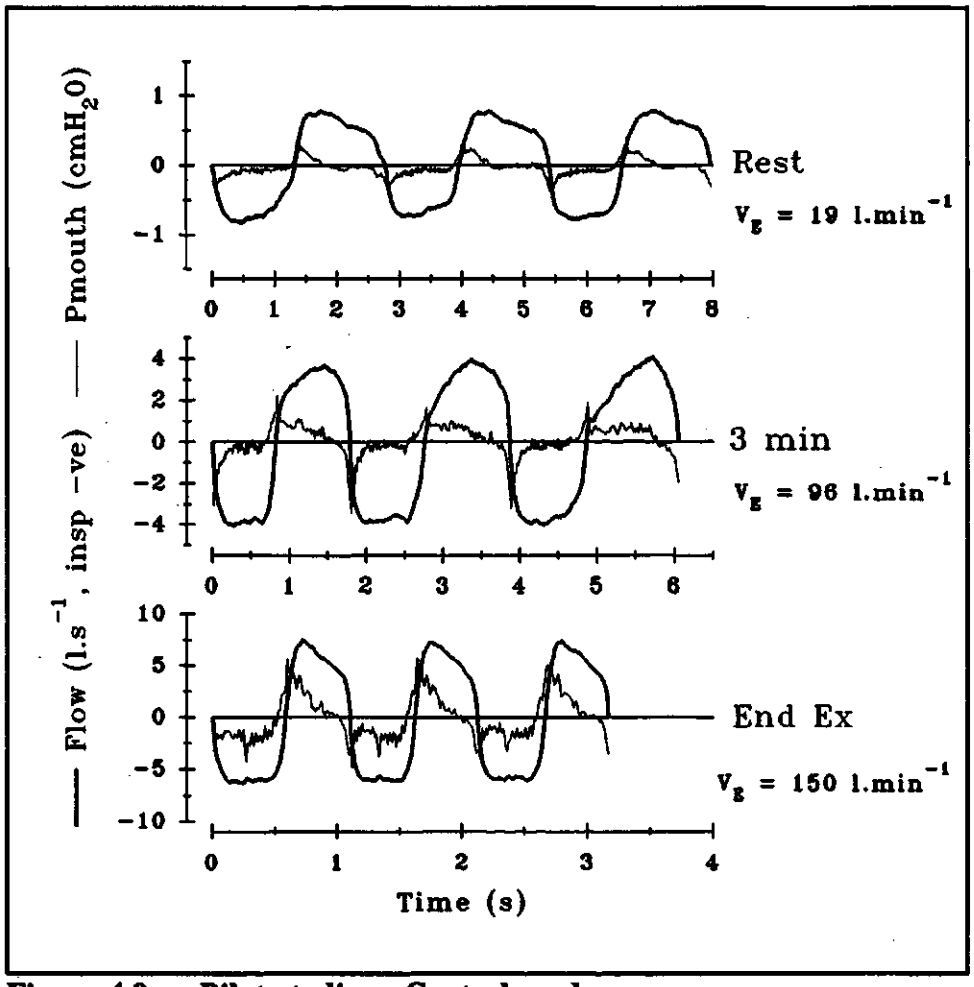

Figure 4.9: Pilot studies - Control mode

exercise, are shown. $\dot{V}E$ levels during these periods are also given. This subject had a high $\dot{V}E$ level at rest (see figure 4.10 also). It is possible that the high minute ventilation at rest could have been due to a combination of factors (anticipation anxiety, effect of a mouth piece etc.). In the control mode the unloader operated to keep Pm near zero. Except for the transient overshoots/undershoots at flow zero crossings Pm through most of exercise was minimal. These transients however increased as $\dot{V}E$ increased (end ex, figure 4.9). The slight resistance (Pm (I) was negative and Pm (E) was positive) observed at end exercise was due to the non-linear resistance of the connecting tubing with higher flow rates.

In the unload mode (figure 4.10) inspiratory Pm was positive except for the first 50 ms when it was slightly negative (Pm lagging $\dot{V}$). A lag between the Pm and $\dot{V}$ signals was present also at the start of expiration (60 - 100 ms). At the low and moderate levels of $\dot{V}E$ (rest and 3 minutes, figure 4.10), the Pm profile was well related to flow, but at higher levels of $\dot{V}E$ (end ex) the Pm waveform suffered distortion. These high levels of $\dot{V}E$ are usually reached by fit subjects towards the end of exercise. The unload (Pm/$\dot{V}$) levels (in parentheses, figure 4.10) were stable

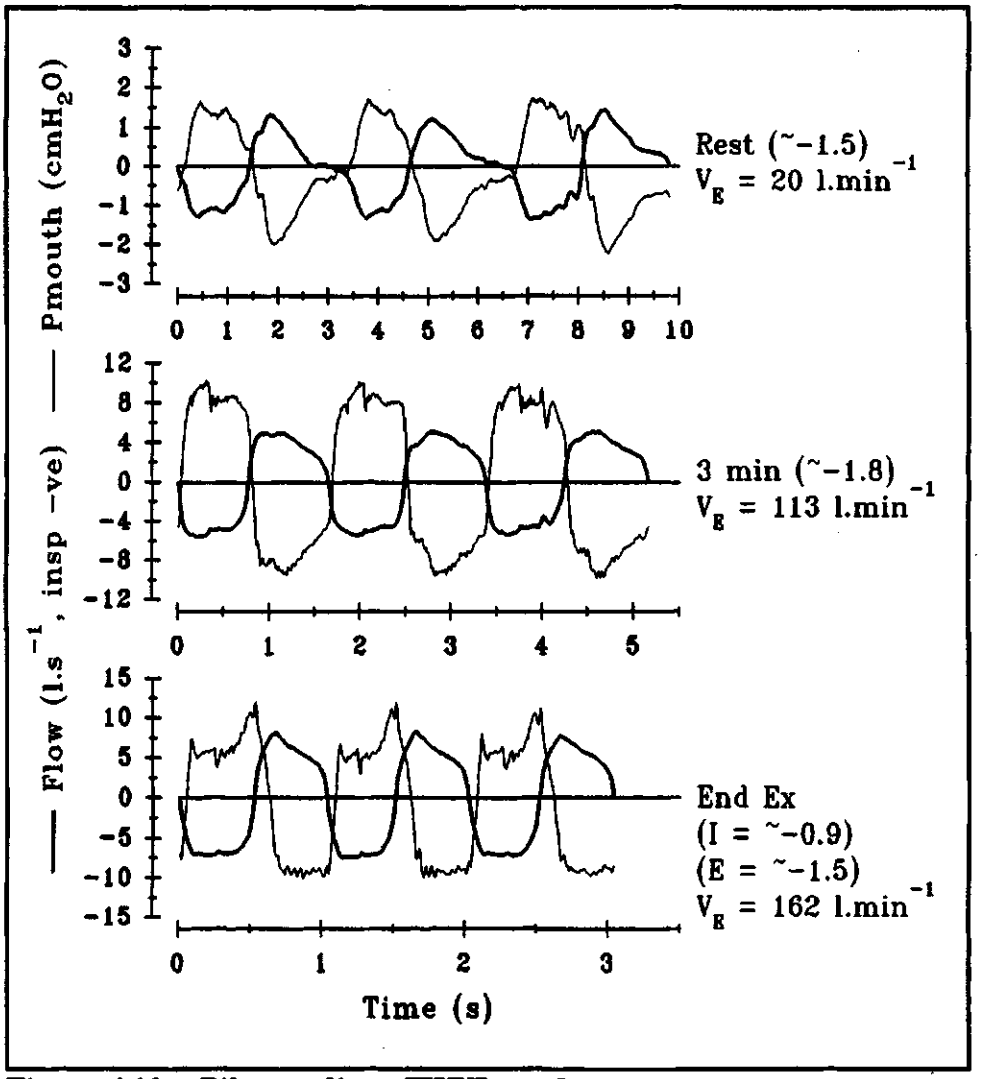

Figure 4.10: Pilot studies - FWUL mode

through most of exercise but became unreliable towards end exercise due to the distortion of the Pm waveform.

The pilot studies revealed other problems in addition to the distortion of the Pm signal with high levels of $\dot{V}E$. The temperature inside the closed system increased progressively throughout exercise. This caused concern as the subjects felt that the increased inspired air temperatures (38 - 42 °C) and humidity could have contributed to their exercise cessation. Temperature increased because warm, humid, expired air was rebreathed before it was cooled. Other factors possibly contributing to the increased temperatures were: the expiratory pneumotachograph which was usually heated to prevent condensation on the resistance elements from the saturated expired air; the exothermic chemical reaction of CO_2 absorption by soda-lime that released heat and water. The humidity inside the closed system had resulted in condensation inside the spirometer chamber. After some of these exercise tests, the rolling seal inside the spirometer was found everted (it had slipped between the piston rim and spirometer's inner wall). This back and forth slippage of the rolling seal occurring on a breath-by-breath basis during exercise could have also contributed to the distortion of the Pm waveform in some subjects. In addition, data analysis from these subjects revealed that $FICO_2$ tended to rise (0.5 - 1%) progressively towards end exercise, due to saturation of the soda-lime (CO_2 absorber). As inspired CO_2 is a potent ventilatory stimulus, this problem needed correction.

4.4 Modifications

The pilot study results revealed that both the quality and the levels of unloading during exercise were quite variable, due to distortion of the Pm waveform

with high levels of $\dot{V}E$ (figure 4.10). A number of modifications in the unloading device and its accessories were required in order to apply reliable, proportional, resistive unloading throughout heavy exercise in normal subjects. A description of these changes is provided in the numerical order shown in figure 4.11. The comparison of figure 4.11 (modifications) with figure 4.7 (original design), highlights the changes that were necessary.

1. ***Prevention of piston distortion***: It was possible that the distortion of the aluminium piston could have either contributed to, or be caused by, the slippage of the rolling seal between the piston rim and the spirometer wall. In order to prevent this from occurring the surface of the piston was reinforced with a '+' shaped piece of aluminium. Subsequent testing showed that the incidence of the rolling seal being everted at the end of exercise, was much less frequent.

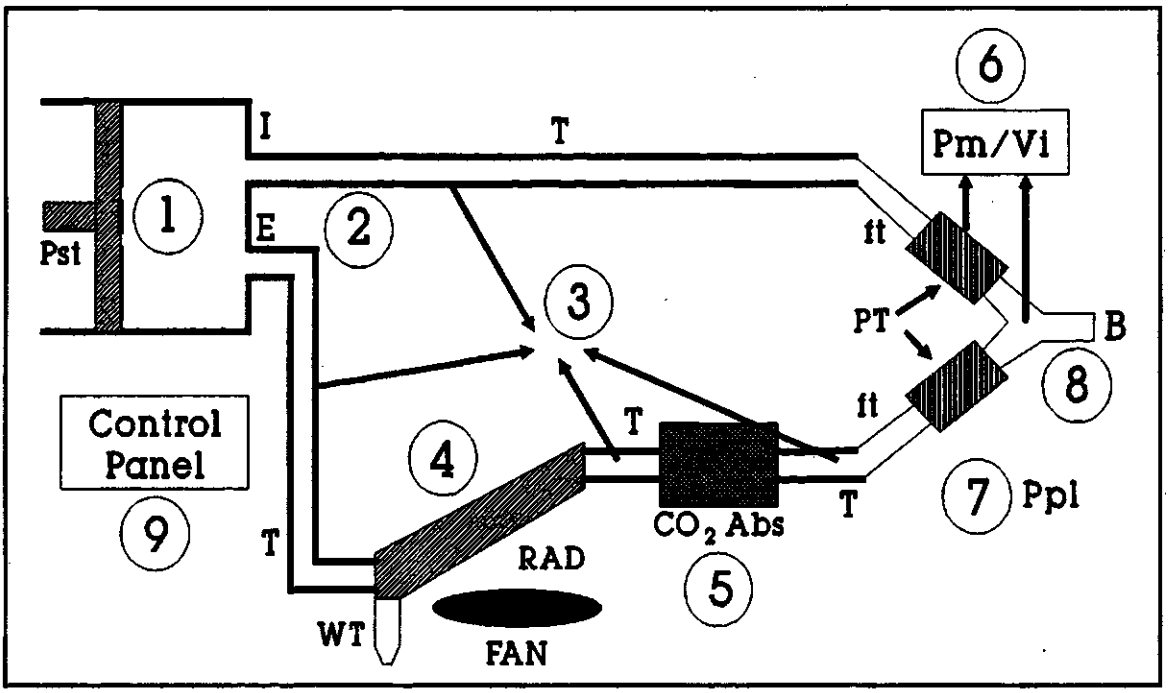

Figure 4.11: Modifications made in the unloading device and accessories

2. ***Separate inspiratory and expiratory ports***: The prototype shown in figure 4.7 had a 'T' shaped common inspiratory and expiratory port connected to the front face of the spirometer chamber. The gas remaining at the distal end of the expiratory limb tended to contaminate the inspirate, as it was not mixing with the spirometer gases (100% O_2 + expirate). This problem was overcome by isolating the inspiratory and expiratory limbs on the front face of the spirometer chamber. The separate inspiratory and expiratory limbs (figure 4.11) enabled the expirate to mix more evenly with the 100% O_2 flowing into the system.

3. ***Wide bore (2" I.D) rigid tubing***: With the exception of a short segment of flexible tubing on either side of the breathing valve/pneumotachometer (to enable free movement with the subject during exercise), all tubing was replaced with rigid 2" ABS plumbing (T). This reduced the resistance and the compliance of the system and ensured rapid conduction of the spirometer pressure to the mouth.

4. ***Radiator and Water trap***: In order to control the inspired air temperature and avoid condensation inside the spirometer chamber, a modified car radiator (RAD) and water trap (W.T) were introduced in the expiratory limb of the system. This cooling system consisted of small parallel tubes (reduced resistance) and was mounted in a slanting manner leading to the water trap at the distal end. An external fan enabled rapid heat exchange between the room and the expired gases in the radiator. The volume of the radiator and its tubes was small (750 ml) and its resistance to air flow was less than 0.5 $cmH_2O \cdot l^{-1} \cdot s$. The inspired air temperature was thus controlled throughout exercise and kept within 2 - 5 $^{\circ}C$ above room temperature, after the installation of the cooling system. The condensate from the radiator (20 -

50 ml) collected in the detachable water trap.

5. ***Effective CO_2 absorption***: The existing CO_2 absorber canister (3.3 l) was replaced with a larger one (6.5 l), thus doubling the amount of soda-lime available for complete CO_2 absorption ($FICO_2 < 0.1\%$) throughout prolonged exercise. The container was filled loosely (to increase surface area and reduce flow resistance) and soda-lime was replaced for each exercise study.

6. ***Monitoring and regulation of the level of unload***: The pilot studies showed that the unload levels were quite variable especially towards end exercise. In order to provide stable physiological unloading throughout exercise, a control over the unload ($Pm/\dot{V}$) levels was desired. An analog divider circuit was designed with Pm and inspiratory flow signals as inputs and its output was calibrated for resistance units ($cmH_2O \cdot l^{-1} \cdot s$). Breath-by-breath $Pm/\dot{V}(I)$ and flow signals were recorded on a two channel analog recorder (Gould). It was thus possible to monitor, and if necessary, increase/decrease unload levels during exercise.

7. ***Measurement of Ppl***: Ppl is a conventionally used index of intrathoracic pressure. It was decided that Ppl could be measured using standard techniques (Milic-Emili *et al*, 1964) throughout exercise in some subjects in order to confirm if unloading of the respiratory muscles had actually occurred. Ppl and other indices (Chest wall resistance, elastance etc., described later) would be used to calculate the mechanical output of the respiratory muscles (P_{mus}), during exercise.

8. ***Replacement of breathing valve***: In order to improve the relation between the Pm and command signals, the distortion of the Pm waveform at higher $\dot{V}E$ levels had to be corrected. One of the possible causes of Pm distortion was discovered to be the

breathing valve used in the pilot studies. Figure 4.12 illustrates the design of the valve (Hans Rudolph #2700) that was used, and its replacement (Y-valve). The Rudolph valve is a 'T' shaped two way valve with latex diaphragms that direct flow. Repeated testing of the unloading device and the new plumbing with and without the diaphragms showed that some of the transients on the Pm waveform could have been due to the diaphragms snapping open with the onset of flow. In addition there was a significant resistance (0.6 $cmH_2O \cdot l^{-1} \cdot s$ @ $\dot{V} = 5\ l \cdot s^{-1}$, *manufacturer's specs*) across the diaphragms (opening pressures). The 'Y' shaped valve (Vacumed #K271) which was used in subsequent tests had similar dimensions and less resistance (0.2 $cmH_2O \cdot l^{-1} \cdot s$ @ $\dot{V} = 5\ l \cdot s^{-1}$). The tricuspid design of its diaphragms enabled their opening smoothly into the flow vortex. The unloading device was tested with the new valve and the result was that the Pm signal was cleaner (fewer transients) and better related to flow even at high levels of $\dot{V}E$.

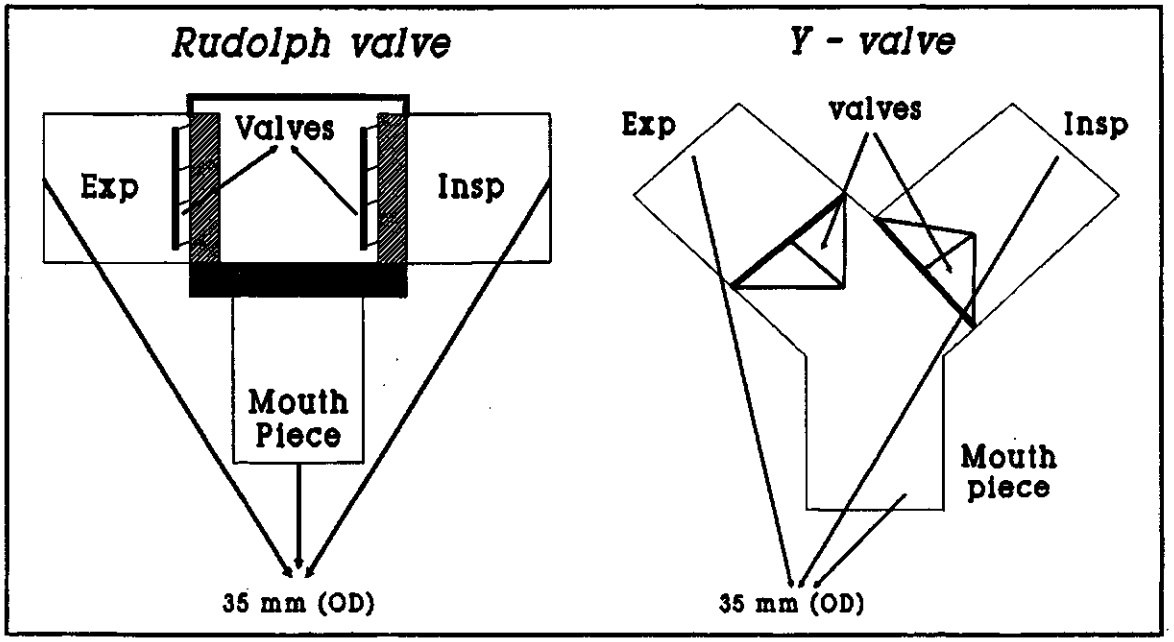

Figure 4.12: Breathing valve designs

9. ***Saturation of the command signal***: It was suspected that electrical saturation of the command signal could have been one of the causes of the Pm distortion. Analysis of the command signal amplifier circuits (Amp 0 - 3.3, figure 4.5) showed that the command signal clipped at higher levels of $\dot{V}$ ($6\ l \cdot s^{-1}$) due to input current saturation. The input resistance (300 Ω) of the command signal amplifier circuit was increased (3.3 KΩ). This changed the gain range of the amplifier circuit from 0 - 33 to 0 - 3.3 and prevented the command signal from clipping with even higher ($8\ l \cdot s^{-1}$) flow rates.

4.5 Evaluation of performance

After all the modifications were made and the individual accessories were tested for optimal performance, the unloading device was reassembled and reevaluated. Pressure response (square wave testing) and animal ventilator studies were repeated and satisfactory results were obtained. It was then set up for FWUL in three volunteer subjects performing constant heavy exercise to exhaustion. The device was primarily tested for the following conditions: (1) the quality of unload (Pm better related to $\dot{V}$), (2) the temperatures inside the closed breathing system throughout prolonged (> 15 min) exercise to assess the cooling system, (3) the ability of the larger CO_2 absorber to keep $FICO_2$ below 0.1% during exercise, (4) to observe the pressure profile inside the spirometer chamber (PSP) to compare it with Pm (5) the stability of unload levels (for a given command signal) throughout exercise.

The data from one test presented here are from a fit subject who exercised for over 40 minutes on the bicycle ergometer at high work rates (250 - 300 watts for

30 minutes and 350 watts thereafter). A resistive unload of 1.8 $cmH_2O \cdot l^{-1} \cdot s$ was desired (75% of the subject's total respiratory resistance) and the command signal amplifier was adjusted early in exercise such that the Pm/$\dot{V}$ was 1.8. Inspiratory and expiratory temperatures were monitored by thermometers on either side of the breathing valve. $\dot{V}$, Pm and PSP were recorded on an 8-channel analog recorder (Gould) and were also sampled at 100 Hz for storage on a computer disk. Table 4.2 and figure 4.13 provide data at 10, 30 and 43 minutes of exercise, in that subject.

Table 4.2: Exercise data (one subject) using the modified unloading device

Time	$\dot{V}E$ ($l \cdot min^{-1}$)	$\dot{V}$ ($l \cdot s^{-1}$) peak		Pm (cmH_2O) peak		PSP (cmH_2O) peak	
		I	E	I	E	I	E
10 min	75	4.7	3.3	8.1	-5.2	12.2	-8.2
30 min	82	5.2	3.7	8.7	-5.8	13.0	-9.4
43 min	116	6.5	5.1	10.6	-8.3	16.0	-12.6

The subject reached and sustained high levels of $\dot{V}E$ throughout exercise. The larger Pm response during inspiration was due to the greater inspiratory flow. The spirometer pressure was well within the maximum output capacity of the device i.e. ± 20 cmH_2O. Figure 4.13 illustrates the $\dot{V}$, Pm and PSP profiles in 3 breaths from the 10th, 30th and 43rd minutes of exercise. The PSP profile followed that of $\dot{V}$ closely, lagging $\dot{V}$ by 20 - 40 ms, both at the start of inspiration and expiration. These delays were possibly due to a combination of linear actuator inertia and compression/decompression of gases inside the spirometer. The Pm profile, positive in inspiration and negative with expiration followed that of flow (CS) very well. The

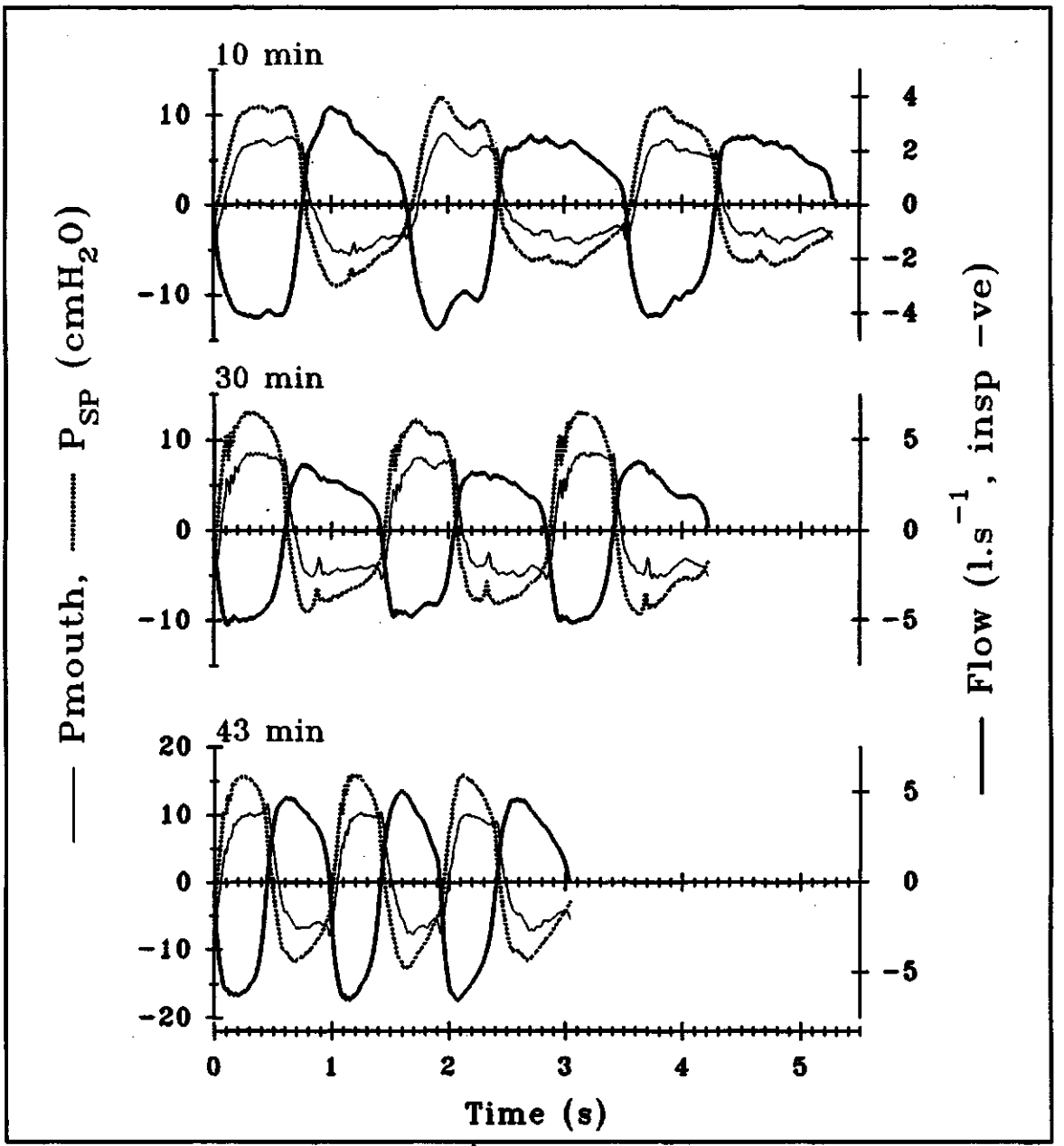

Figure 4.13: Unloader evaluation - $\dot{V}$, Pm and PSP signals

high frequency transients seen (in the pilot study results) at flow transitions were also reduced. The short delays (60 - 90 ms) between Pm and $\dot{V}$ were however greater than those between PSP and $\dot{V}$. This could have been due to the tubing resistance and accessories (CO_2 absorber, radiator, breathing valves etc.) as well as due to compression effects. Table 4.3 summarises the delays and the unload levels recorded

during these periods in the same subject.

Figure 4.14 shows $\dot{V}E$, $FICO_2$, inspiratory and expiratory unload levels throughout exercise in the same subject. $\dot{V}E$ increased and $FICO_2$ was less than 0.1% throughout the exercise duration (43 minutes). Unload levels (I and E) remained steady (~ 1.8 $cmH_2O \cdot l^{-1} \cdot s$) through most of exercise.

Table 4.3: Unload levels and lag times during exercise after modifications

Time	Lag (msec)				Unload ($cmH_2O \cdot l^{-1} \cdot s$)	
	$\dot{V} \leftrightarrow Pm$		$\dot{V} \leftrightarrow PSP$			
	I → E	E → I	I → E	E → I	I	E
10 min	82	93	22	43	-1.7	-1.8
30 min	72	67	20	37	-1.7	-1.7
43 min	90	65	35	30	-1.6	-1.7

The slight tendency for the unload levels to drop towards end exercise, could however be offset by adjusting the command signal gain. Temperatures inside the closed system were well controlled throughout this exercise test (2 - 5 °C above ambient temperature).

4.6 Measurement of the volume of the system

In order to calculate oxygen uptake of the exercising subjects, the changes in FIO_2 had to be converted to O_2 volume (by mass-balance principles). The volume of the closed breathing system (Unloading device + accessories) had to be measured to calculate the dilution factor *k* required to convert changes in O_2 concentration to O_2 volume. This measurement was done after ensuring that the device was leak free (static pressure testing).

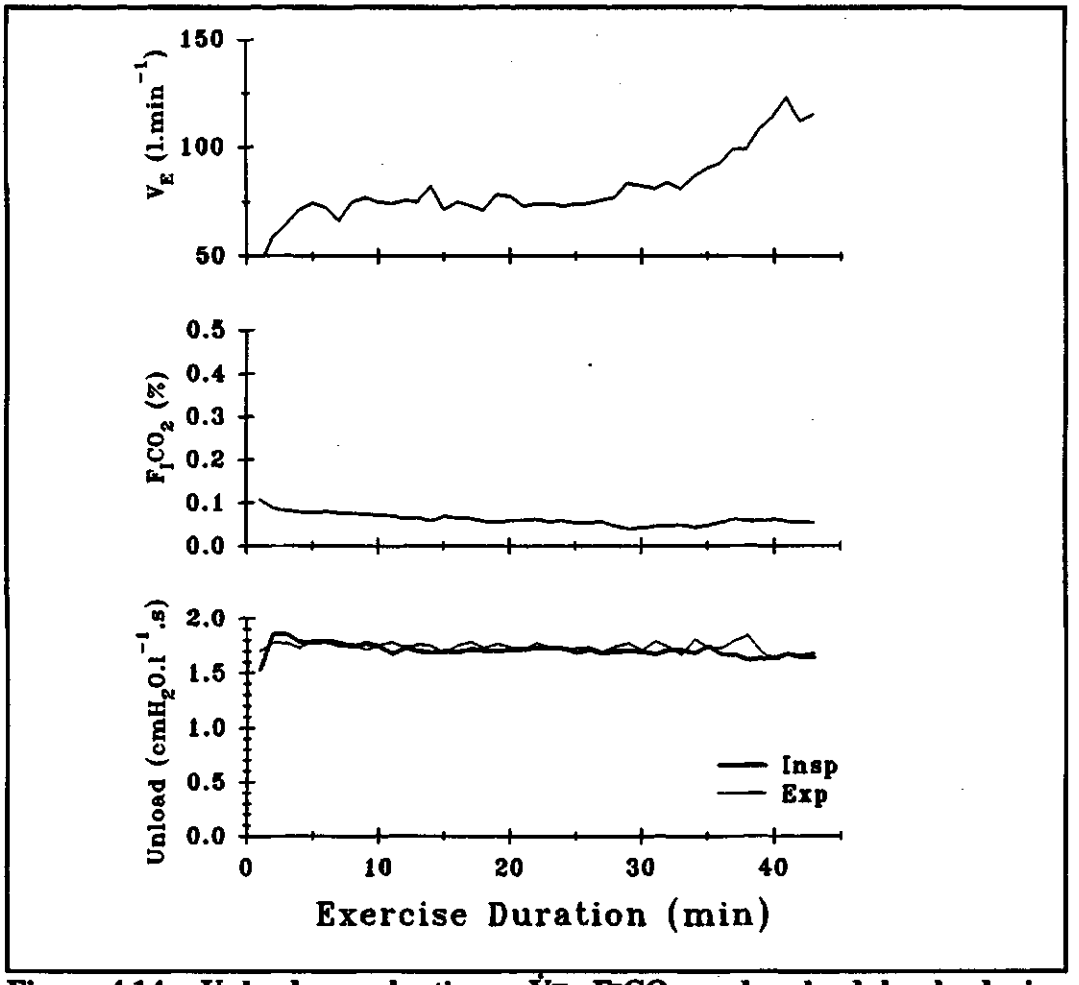

Figure 4.14: Unloader evaluation - $\dot{V}E$, $FICO_2$ and unload levels during exercise

Known volumes of O_2 (measured with pneumotachometer/transducer (Fleisch #3/Validyne MP45 ± 2cmH_2O) were added into the system when it was passively ventilated with a pump and the changes in O_2 concentration were noted. The calculated volume of the closed system was 19.5 l. The calculated value of *k* was further corrected to take the lung volume of the subject into account. It was assumed that for every 1% increase in FIO_2, alveolar O_2 concentration would also increase by 1%. The recalculated *k* (assuming the subject's alveolar volume of 4 l) was 297 cc of O_2 for 1% change in FIO_2.

4.7 Summary

A versatile loading/unloading device that was developed recently [Younes *et al*, 1987] was described. The objective of this thesis was to set up and test a prototype of this device for full wave resistive respiratory muscle unloading in normal human subjects performing prolonged exercise to exhaustion. Initial tests for pressure response and pilot unloading studies on human volunteers revealed a number of problems that required correction. Many modifications to the existing device and its accessories were necessary for its optimal performance in exercise. A detailed description of these changes was presented. The device and its accessories were reassembled after modifications and tested again for its ability to apply FWUL in exercising subjects. The results of the tests showed that the modified unloading device was able to apply reliable, proportional resistive unloading to the respiratory muscles throughout exercise in fit subjects.

5. STUDY DESIGN

5.1 Introduction

The role of mechanical factors in the control of exercise ventilation has been of interest to many researchers in the past. Some of the mechanical adjustments that take place in the respiratory pump during exercise were reviewed in chapter 2. It has been questioned if respiratory muscle fatigue (if it occurs) could contribute to exercise limitation. Many techniques have been employed to address these issues. In most cases, the load on the respiratory system was altered to study the role of mechanical factors on exercise ventilation. A recently developed loading/unloading device has enabled researchers to apply a variety of loads/unloads both at rest and during exercise in human subjects. A prototype of this device was evaluated and successfully modified (by this author) for use in prolonged heavy exercise. This chapter describes a study design to examine the effects of FWUL on exercise performance.

In a previous study [Gallagher and Younes, 1989] the unloading device was used to apply inspiratory resistive unloading (fixed levels, 2.2 $cmH_2O \cdot l^{-1} \cdot s$) in normal subjects performing incremental exercise to exhaustion. The study was designed to examine if inspiratory unloading relieved post-exercise tachypnea (rapid breathing pattern), which has been linked to inspiratory muscle fatigue. The authors reported that there was no difference in either exercise breathing pattern or duration, between the two tests. In another protocol in the same study, FWUL (fixed levels, 2.2 $cmH_2O \cdot l^{-1} \cdot s$) was applied intermittently (2 minutes) alternating with control

periods (2 minutes) over 12 minutes of constant work-rate exercise (70 - 80% $\dot{V}O_2max$). Although there was no difference in the ventilatory pattern between the two periods, the authors documented a 20% fall in inspiratory motor output ($P_{mus}(I)$, discussed later) with FWUL.

The present study was designed to approach this problem differently. The hypothesis tested here was that if respiratory muscle fatigue contributed to exercise limitation, then reducing muscle work throughout exercise, improves tolerance (increases duration). The unloading device was set-up to apply proportional FWUL throughout heavy exercise, in normal subjects. The subjects participating in this study had to be motivated and capable of performing high intensity exercise to exhaustion. The constant work-rate chosen ($\sim$90% $\dot{V}O_2max$) for these subjects would not only ensure a high $\dot{V}E$ response early in exercise but also was high enough that exercise did not continue indefinitely. These factors were taken into consideration in order to avoid day to day variability as well as to ensure a fixed end point (exercise duration) for comparison between the control and FWUL tests. The two tests (control and FWUL) were randomised (test order) to account for variability due to learning effects, among the subjects. In order to confirm if respiratory muscle unloading was occurring, Ppl was measured in five of the seven subjects during exercise on both days.

5.2 Methods

Seven healthy male subjects (20 - 30 years) consented to take part in the study. The subjects were interviewed and completed an exercise questionnaire (Appendix A). All the subjects were well motivated and were used to some form of

regular exercise. They had a normal physical examination and electrocardiogram. Although the subjects gave informed consent, none was aware of the specific goals of the study. After assessing the subjects' suitability for the study, initial measurements of peak exercise $\dot{V}O_2$, practice submaximal endurance time, Raw and Elw, were made.

5.2.1 Assessment of peak exercise $\dot{V}O_2$ and endurance capacity

Each subject underwent an initial incremental exercise test to exhaustion to measure peak exercise $\dot{V}O_2$ and maximum exercise capacity. The subjects exercised on a bicycle ergometer. The work load was increased incrementally (25 watts every minute) after two minutes of warm up at 50 watts. $\dot{V}E$, VT, f, HR, $\dot{V}O_2$ and $\dot{V}CO_2$ were recorded continuously and measured during the last minute. Three days after the incremental exercise test, each subject performed a practice constant work-rate (at 80 - 90% of maximum work-rate) exercise to exhaustion. This was done to assess the subject's ability for endurance exercise and his motivation. It also helped in familiarising the subject with the protocol of constant work rate exercise. It was thus possible for us to estimate the work load at which the control and unload tests should be performed, for each subject. The work rate (chapter 6) chosen for each subject represented the level that elicited approximately 90% of his peak exercise $\dot{V}O_2$, and one at which the subject had a high ventilatory response that could be sustained for over 10 minutes.

5.2.2 Measurement of Raw

It was necessary to measure Raw, to estimate the level of resistive unloading for each subject. As discussed in chapter 2, Raw is the ratio of the difference

between Pm and P_A to $\dot{V}$. The resistance of the chest wall (Rw) in normal subjects is about 1.0 $cmH_2O \cdot l^{-1} \cdot s$ [Mead and Agostini, 1964., Aronsson *et al*, 1977]. It was intended to use an unloading level of ~75% of sum of chest wall and lung tissue resistance, for all subjects. Raw was measured in a constant-volume-variable-pressure body plethysmograph, using a conventional technique [DuBois *et al*, 1956]. The subject sat comfortably in a sealed constant volume plethysmograph (Cardio-Pulmonary Instruments Model 2000, figure 5.1). $\dot{V}$, Pm and box pressure (P_{BOX}) were measured. The technique assumes that with the airway occluded, changes in P_{BOX} reflect changes in P_A accurately (Boyle's law).

After two minutes of quiet breathing the subject was instructed to pant rapidly (~1 Hz). Two X - Y plots were made on the oscilloscope screen and stored: **(A)** a plot of $\dot{V}$ versus P_{BOX} with the mouth piece shutter open and **(B)** a plot of Pm versus P_{BOX} (with the shutter closed, $\dot{V} = 0$, figure 5.1). Raw (@ 0.5 $l \cdot s^{-1}$ flow) was

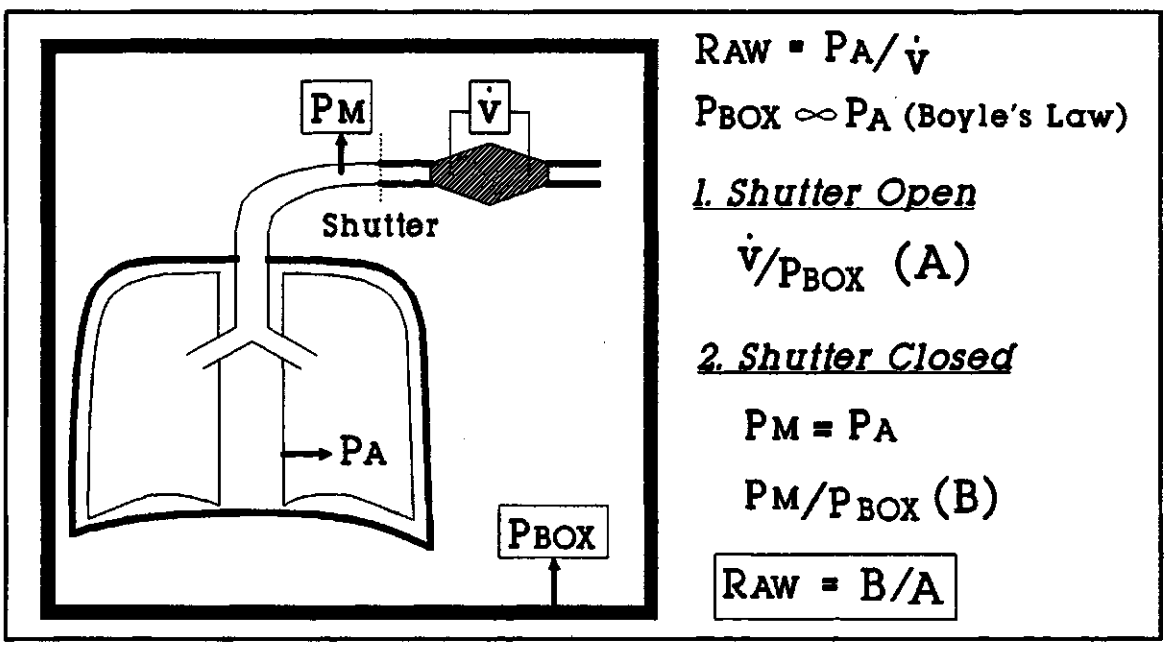

Figure 5.1: Raw measurements using a body plethysmograph

calculated from the slopes of the two plots.

$$R_{aw} = \frac{Pm}{P_{BOX}} \div \frac{\dot{V}}{P_{BOX}} \qquad (1)$$
$$(B) \quad (A)$$

The manoeuvre was repeated until 3 consistent measurements were made. The box was vented between manoeuvres, to balance the box pressure zero (which tended to drift because of increasing temperature).

5.2.3 Measurement of Elw

The motor output of the respiratory muscles (P_{mus}) was calculated (discussed later) using the values of Ppl, $\dot{V}$, and the elastic pressure losses across the chest wall. Elw was measured in five subjects (in whom Ppl was to be measured during exercise), to derive the elastic pressure losses at any given lung volume using the relaxation technique [Rahn *et al*, 1946]. The subjects were trained to relax against a closed airway. This was achieved by using a manually controlled shutter in the breathing apparatus. After a brief period of training the subjects were able to relax satisfactorily against the occlusion at various lung volumes below TLC. The manoeuvre was repeated several times and only the reproducible and relaxed measurements were used to construct a curve of chest wall recoil against lung volume. That the subject was relaxed was ascertained from the simultaneous observation of Ppl and Pm. There were no abrupt changes or artifacts in either of the signals, and a steady plateauing of the Ppl signal at each lung volume step was observed. At any given lung volume the pressure across the chest wall is the

difference between Ppl and Pbar (= Ppl, Pbar is the reference). If the subject is relaxed (Pmus = 0) and if there are no resistive losses across the chest wall ($\dot{V}$ = 0, airway occluded), then PelW = Ppl. Elw therefore is the relation between the volume and Ppl changes. The data from three relaxed manoeuvres in one subject are shown in figure 5.2. Elw is the inverse of slope of the best fit line (r^2 = 0.96) and is 5.7 $cmH_2O \cdot l^{-1}$ for this subject. Inspiratory muscle strength (PSTR(I)) was measured at various lung volumes using conventional techniques [Rahn *et al*, 1946., Wang *et al*, 1991]. Volumes were measured using a pneumotachometer - integrator system. Ppl was measured using a standard technique [Milic-Emili *et al*, 1964].

5.2.4 Control and Unloading exercise studies

The loading/unloading device and its accessories were then set up for the

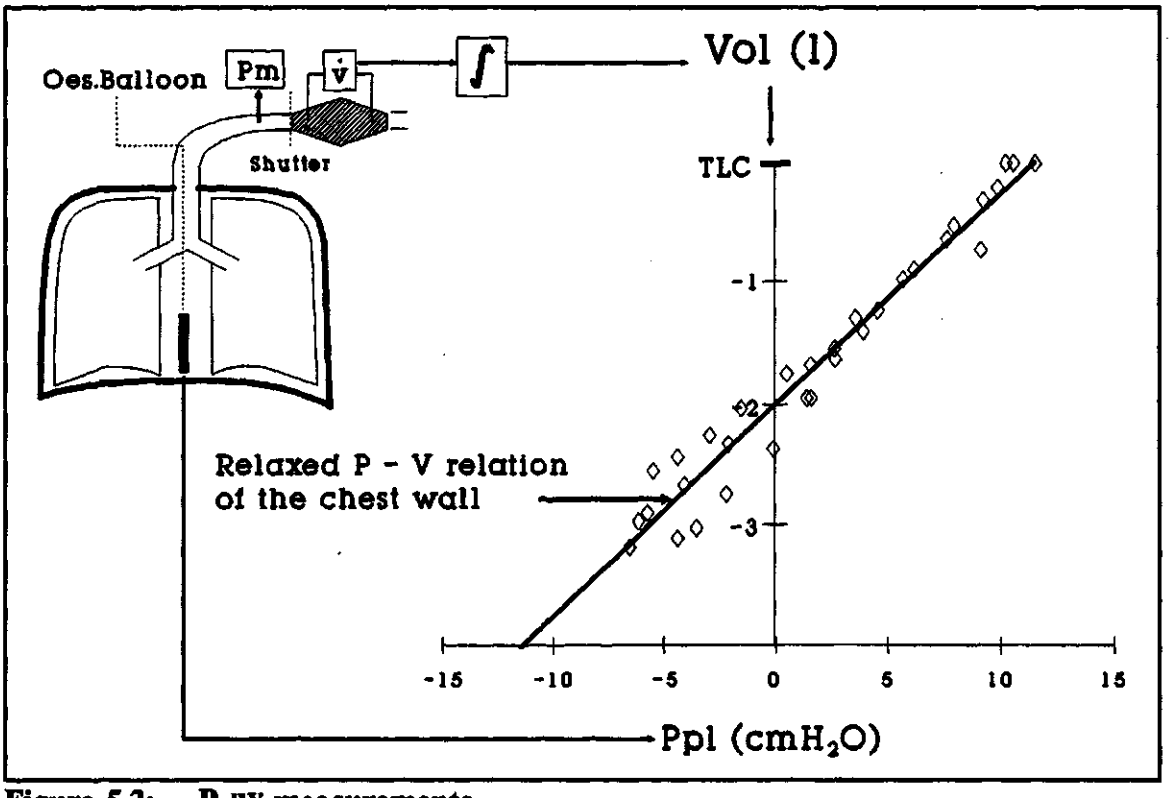

Figure 5.2: PelW measurements

control and unload tests, as shown in figure 5.3.

5.2.4.1 Protocol

The seven subjects performed constant load (@ ~90% $\dot{V}O_{2\ max}$) heavy exercise to exhaustion on two days. These tests were done at least three days after the submaximal practice exercise tests, with the subject two hours in the post-absorptive state. The subjects were also instructed to refrain from any other form of physical exercise and caffeinated beverages before the study. The subject first relaxed and swallowed an oesophageal balloon under topical anaesthesia. The balloon, connected to a pressure transducer (Validyne MP45, ± 140 cmH_2O) was zero-balanced with a small amount (< 2ml) of air. It was then positioned in the

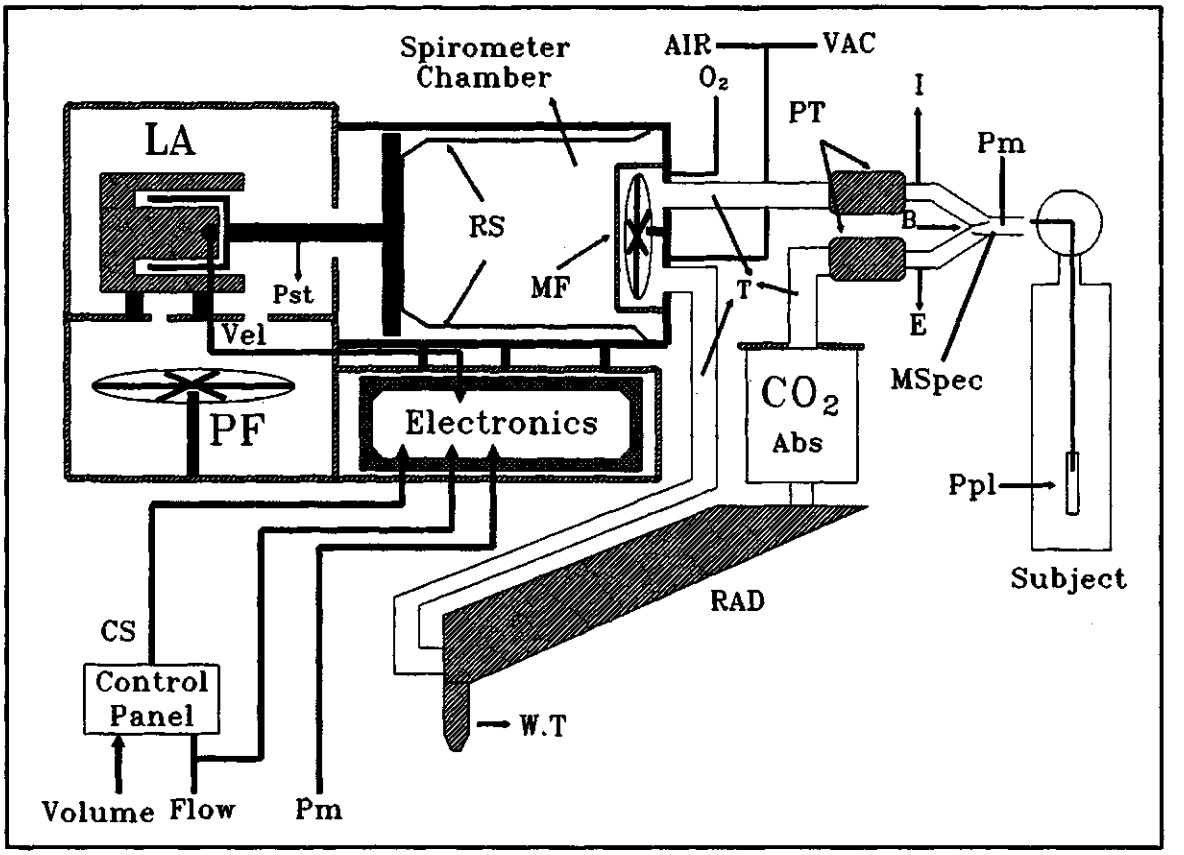

Figure 5.3: The modified loading/unloading device

oesophagus where the best Ppl signal (most negative at end expiration and with the least cardiogenic artifacts) was observed [Wang *et al*, 1991]. The subject then mounted the exercise bike and was familiarised with making an inspiratory capacity (IC) manoeuvre (inspiration to total lung capacity).

The subject then breathed quietly on the mouthpiece for two minutes. The unloading device was turned on to the control/unload mode. The subject was previously cautioned about the slight pressure that he might feel at the mouth during unloading. However, none of the subjects felt that it hindered their normal breathing. The subject was instructed to pedal at 50 watts (50 -70 rpm) for two more minutes (warm up). At that point, with the subject alerted, the work rate was abruptly raised to a load that represented ~90% of his peak $\dot{V}O_2$. The same set of instructions were given to the subject on both the control and FWUL days. He then continued to pedal against this work load until he could do no more. At the end of every two minutes the subject was instructed to perform an IC manoeuvre and hold his breath for about one second. Exercise duration was recorded on a stop-watch as the time between commencement of exercise at the high work-load and exercise cessation.

5.2.4.2 Signals and connections

Inspiratory and expiratory flows were measured using two separate pneumotachometers/transducers (Fleisch #3/Validyne MP45, ± 2cmH_2O), on either side of the breathing valve. The two signals were then added electronically to provide flow throughout the respiratory cycle. The flow signals were calibrated using a 4 l precision syringe, at rates of 2 - 6 $l \cdot s^{-1}$ and filtered at 50 Hz. The individual

$\dot{V}$ zeroes were monitored at a high gain on an oscilloscope throughout exercise in order to correct for drift whenever it occurred. Flow was integrated to provide volume. Pm was measured at a port in the mouthpiece, using a pressure transducer (± 30 cmH_2O)/demodulator system (Validyne). The Pm signal was calibrated and filtered at 50 Hz. Both the mouth and oesophageal pressure transducers were calibrated against a water manometer. The Pm and the inspiratory flow ($\dot{V}_I$) signals were the inputs to the analog divider circuit, the output (resistance) of which was recorded on a two channel recorder (Gould, model 220), in order to correct for any breath-by-breath drift in the level of unload. This signal was previously calibrated for resistance units.

Oxygen flow into the closed system was measured using a Fleisch pneumotachometer and transducer (± 2 cmH_2O)/demodulator system (Validyne). The O_2 flow signal was calibrated at rates of 30 - 60 $ml \cdot s^{-1}$ using a precision 60 ml syringe, and integrated to provide volume. The O_2 flow tubing was connected to the front face of the spirometer chamber behind the mixing fan. Inspired and expired O_2 and CO_2 concentrations were measured at the mouth on a breath-by-breath basis using a mass spectrometer (MSpec Figure 5.3, by Airspec, model 2000FF). The F_{IO_2} signal was displayed graphically on a screen and monitored by an investigator who had the instantaneous O_2 flow signal also available such that FIO_2 was controlled at around 21 ± 2%.

The volume of air in the closed system had to be controlled in such a way that the subject's tidal volume was always within the limits of spirometer volume (V_{SP}, ~6 litres). This was done by keeping the signal from the potentiometer (tracking

spirometer piston position) within the "full" and "empty" marks on an oscilloscope screen (Nicolet, model 2090-III) by either adding compressed air or by operating a vacuum pump. The operator thus maintained the subject's V_T well within the limits of the system. He also operated a switch which marked on the recorder the times when this intervention was necessary so that gas measurements were not made during those intervals. Inspired and expired temperatures were recorded using thermometers on either side of the breathing valve. Electrocardiogram was recorded using standard leads.

The experimental layout and the relevant signal routes are illustrated in figure 5.4. The signals were routed to their appropriate connections. $\dot{V}$, V, O_2vol, Pm, Ppl, FIO_2, EKG and V_{SP} signals were recorded on an 8-channel recorder (Gould, Model 8188-8810). The control panel received $\dot{V}$ as its input. The output of the control

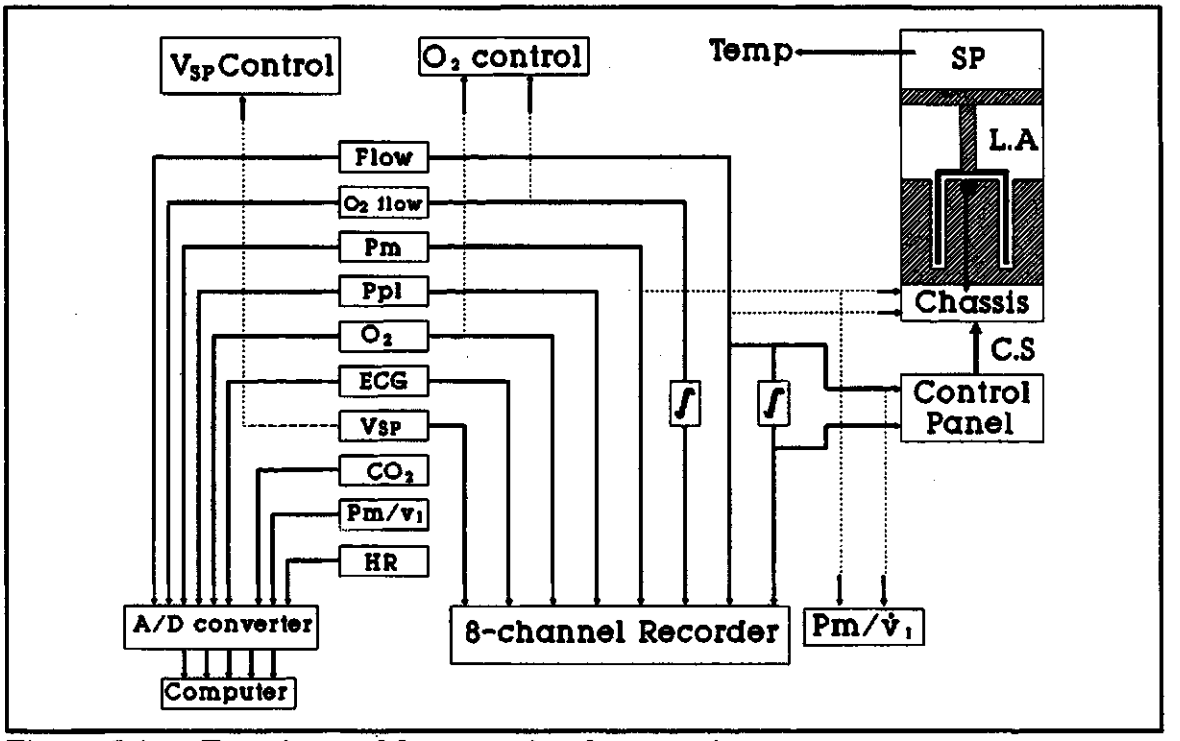

Figure 5.4: Experimental layout - signal connections

panel (CS), Pm, $\dot{V}$ and V signals were connected to appropriate unloading device inputs. All the above signals, F_ETCO_2, HR, and $Pm/\dot{V}_I$ were also sampled at 100 Hz and digitised (PCI - 20000, 16 channel, 12 bit A/D converter) for storage on a computer disk. All the equipment and transducers were calibrated before and after each experiment.

5.2.4.3 Data analysis

The digitally stored data were replayed on a computer screen using software developed in our laboratory. The onset and the end of both inspiratory and expiratory flows were identified by the computer, and all breaths except those interrupted by coughing or swallowing were counted and labelled. The computer then calculated T_I and T_E for each breath. $V_T(I)$ and $V_T(E)$ were obtained by digital integration of the flow signal. Ventilatory variables ($\dot{V}_E$, V_T, f) were thus calculated for each minute of exercise. Based on the flow signal (whether I or E), every other signal could be reconstructed breath-by-breath using 200 points (100 each for T_I and T_E) sampled by the computer. An average waveform of any signal (e.g flow) could then be drawn using one or many breaths (usually 20 - 30) for each minute of exercise. The software also provided some summary statistics of the peak and mean values of the breaths that were used in the averaging process. We assessed the temporal course of respiratory muscle pressure (P_{mus}) for every minute of the constant load heavy exercise in five subjects. The method used to derive P_{mus} is based on previous techniques [Younes and Kivinen, 1984., Gallagher and Younes, 1989].

At any instant the pressure across the chest wall (P_w) is the difference

between Pbar and Ppl. With Pbar as reference, Pw = -Ppl. Pw represents the pressures generated by chest wall muscles (Pmus) less the pressure used to overcome the resistance of the chest wall (PresW) and the pressure used to overcome the passive elastance of the chest wall (PelW).

$$Pw = -Ppl = Pmus - PresW - PelW \quad (2)$$

or

$$Pmus = PresW + PelW - Ppl \quad (3)$$

The average time course of $\dot{V}$, V and Ppl for each minute of the constant load exercise, was obtained from the computer. Pmus was calculated at 100 inspiratory (1% TI) and 100 expiratory (1% TE) points using the average values for $\dot{V}$, V and Ppl. Figure 5.5 illustrates the data obtained from one subject and the method used

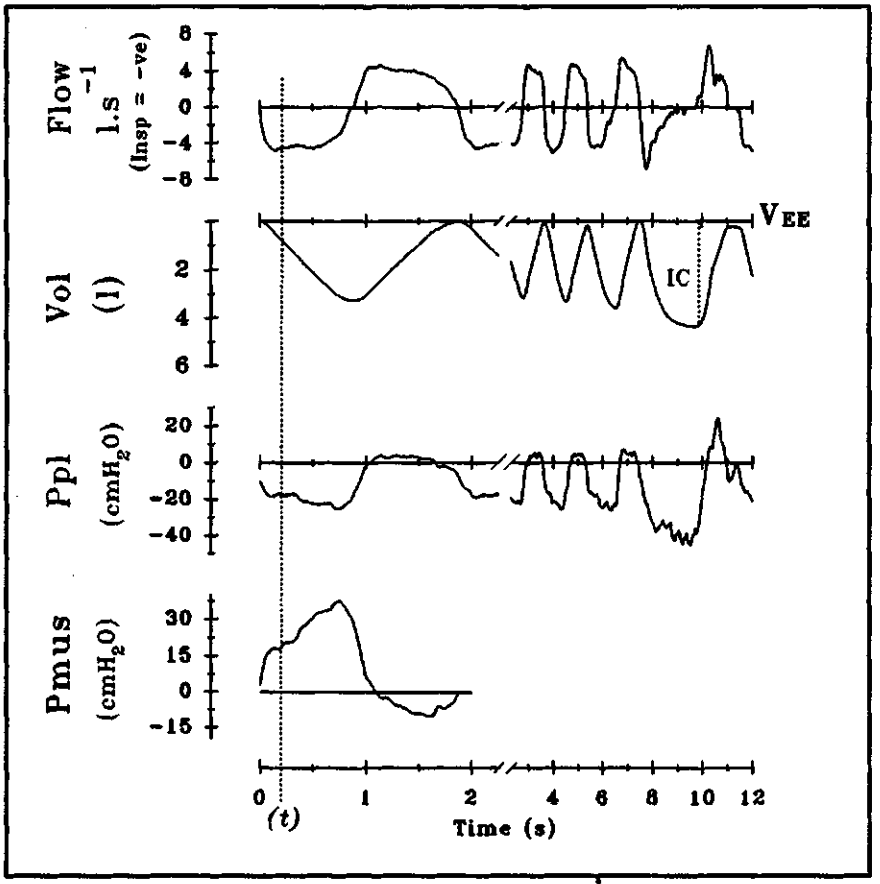

Figure 5.5: Derivation of Pmus(t) using $\dot{V}(t)$, V(t) and Ppl(t)

to calculate Pmus for one breath. At each point t, $P_{resW}(t) = \dot{V}(t) \cdot R_w$, where $\dot{V}(t)$ is the flow at that instant. A value of 1.0 $cmH_2O \cdot l^{-1} \cdot s$ representing the average normal value for Rw [Mead and Agostini, 1964., Aronsson *et al*, 1977], was used. $P_{elW}(t) = V(t) \cdot E_{lw} + P_{elW}(V_{EE})$, where $V(t)$ is the volume above end expiratory lung volume (VEE), Elw the measured chest wall elastance and PelW(VEE). PelW(VEE) was the pressure across the relaxed chest wall and was obtained from end-expiratory Ppl values at rest. VEE was obtained from ICs measured during exercise. Peak and mean (I and E) PMUS values were calculated on a spreadsheet (Microsoft Excel).

5.3 Summary

The protocol designed to study the effects of full wave resistive unloading on exercise performance has been described. The principles involved, and the techniques used in the initial assessment of maximal exercise and endurance capacity, airway resistance, and chest wall elastance in our subjects have been explained. All the measurements made, the signals acquired for analysis and the principles involved in the calculation of respiratory motor output on a breath-by-breath basis throughout exercise have been described. Most of the signals were analyzed using software developed in our laboratory. The details of the results obtained, their physiological and statistical importance are discussed in the next chapter.

6. RESULTS AND DISCUSSION

6.1 Introduction

The results of FWUL and its effects on endurance exercise performance are discussed in this chapter. Initially, the performance of the unloading device during heavy exercise is examined. In the following sections, details of ventilatory pattern (in all subjects) and respiratory mechanics (in five subjects) in both tests are provided. This study examined the evolution of respiratory motor output with and without FWUL and provides some clues to the role of respiratory muscle fatigue in constant work-rate exercise limitation.

6.2 FWUL during heavy exercise

Figure 6.1 illustrates $\dot{V}$, Pm and Pm/$\dot{V}$ signals during heavy exercise in one subject (subject 2). Breath-by-breath data from both the control and the FWUL tests are shown; at 50% of the control test duration (9 minutes); at matched time (18 minutes) i.e. the end of exercise data from the shorter test was matched with data at the same time in the other test; at end exercise in the FWUL test (24 minutes). $\dot{V}E$ levels during these periods are in parentheses. Pm was minimal throughout the control test except for overshoots around flow transition points, due to plumbing and compression of gas in the system.

In the unload mode Pm was positive with inspiration and negative with expiration. Data at 9 minutes of heavy exercise (top right, figure 6.1) show the typical system response at these high $\dot{V}E$ levels (135 $l \cdot min^{-1}$). The inherent mechanical delays in the system caused Pm to lag behind $\dot{V}$ by about 65 - 75 ms.

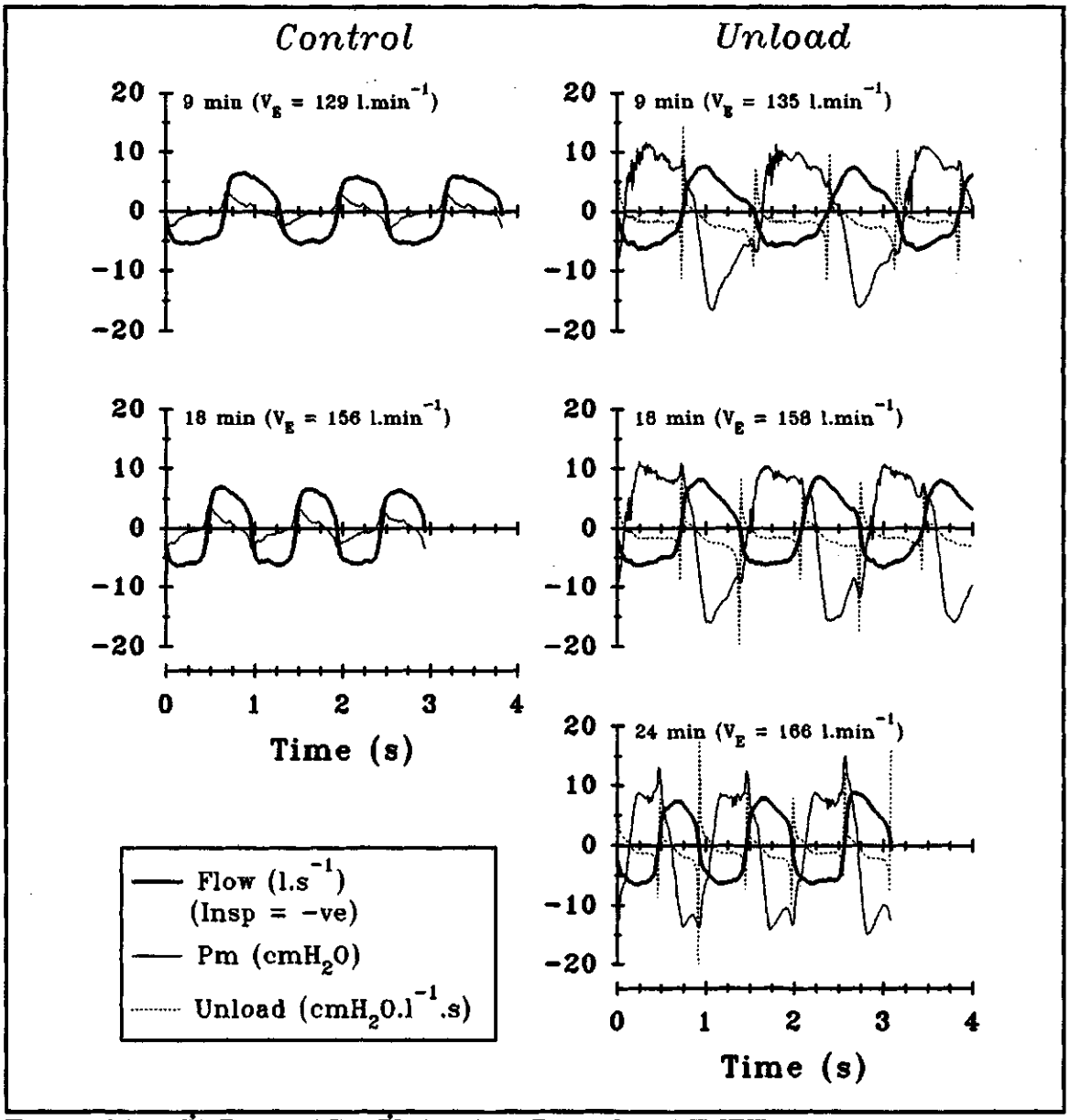

Figure 6.1: $\dot{V}$, Pm and Pm/$\dot{V}$ signals - Control and FWUL tests

Some oscillations in the Pm waveform at the start of inspiration were seen. These were over a short segment of inspiration (noisy flow at these $\dot{V}E$ levels), self-limiting and were controlled with increases in the external NV feedback. The overall Pm profile resembled flow (on which it was based) closely. Unloading at higher $\dot{V}E$ levels (158 l· min^{-1}) seen at 18 minutes was satisfactory. The quality of unloading at end exercise (24 minutes) however was compromised due to some Pm distortion. The

subject did not increase his ventilation significantly (166 l· min^{-1}) but his rapid breathing frequency (~60/min) resulted in quick changes (~every 0.5 sec) in flow direction with a near square wave inspiratory flow pattern. This combined with equipment inertia and compression effects inside the closed breathing system probably contributed to the Pm distortion. The performance of the unloading device and the level of unloading provided in the other subjects were similarly satisfactory. Table 6.1 provides the level of unloading applied in all subjects. These levels were proportional to the subjects' chest wall + lung resistances, and were within the pressure generating capabilities of the device (± 20 cmH_2O).

Table 6.1: Individual subject characteristics and exercise data

Subj. No.	Age (yr)	Height (cm)	$\dot{V}O_2max$		RTOT	Unload	submax workload (watts)
			(l· min^{-1}) STPD	(% pred)	(cmH_2O· l^{-1}· s)		
1	25	165	4.45	119	3.00	-1.78	310
2	23	175	3.86	120	2.57	-1.79	290
3	23	184	3.91	91	1.98	-1.76	280
4	26	181	3.33	118	2.61	-1.56	190
5	27	180	4.15	103	2.67	-1.73	280
6	20	183	2.96	85	2.13	-1.68	230
7	21	180	3.73	87	2.25	-1.67	220
mean	24	178	3.77	103	2.46	-1.71	257
SE	1	2	0.2	6	0.13	0.03	16

$\dot{V}O_2max$, % predicted values [Jones and Campbell, 1982];

The seven subjects studied reached high $\dot{V}E$ levels and sustained them throughout exercise (~110 l· min^{-1} @ 50% of control duration). The average

resistance (unload) during the FWUL test was -1.71 $cmH_2O \cdot l^{-1} \cdot s$ (table 6.1) and during the control test 0.3 $cmH_2O \cdot l^{-1} \cdot s$. The net unload therefore was -2.01 $cmH_2O \cdot l^{-1} \cdot s$. Hence with unloading, ~73% of the total (subject + equipment) resistance was unloaded during I and E throughout exercise.

6.3 The effect of resistive unloading on exercise performance

Table 6.1 contains individual subject characteristics and exercise performance data. The mean (± SE) for the group is also given. The subjects were moderately fit (~103% $\dot{V}O_2$ predicted), well motivated and completed the constant work rate exercise (~80% max) on both the control and unload days without difficulty. On termination of exercise the subjects reported the level of breathlessness (dyspnoea) and the leg discomfort/pain felt on a scale of perceived exertion (appendix B) [Borg, 1982] and the reason for stopping exercise (dyspnoea and/or leg pain). Although the subjects reported a significant level of dyspnoea at the end of exercise, most of them said they stopped exercise because of leg pain/discomfort. Table 6.2 summarises the details of Borg scores and exercise duration in the two tests. Paired *t* testing revealed that there was no significant difference in either total exercise duration nor the Borg scores at end exercise, between the control and FWUL tests.

6.3.1 Ventilatory variables

Data from each minute of constant work load exercise was analyzed in all subjects. A minimum of 25 breaths were chosen and averaged. The computer provided VT (digital integration of expiratory $\dot{V}$), TI and TE. $\dot{V}E$ and TI/TTOT were calculated from these data. F_ETCO_2 and FIO_2 (%) was obtained from the breath-by-breath mass spectrometer output. HR and IC (5 subjects) were measured from the

paper record. O_2 consumption ($\dot{V}O_2$) every minute was estimated according to mass balance principles: $\dot{V}O_2$ (ATPD[1]) = O_2 vol - $k \cdot \Delta FIO_2$ (see chapter 4). O_2 vol was the amount of 100% O_2 added to the system (integrated O_2 flow, ATPD). ΔFIO_2 (the change in system O_2 concentration) and k were used to convert O_2 concentration to volume. $\dot{V}O_2$ (ATPD) was converted to STPD[2] values [Jones and Campbell, 1982].

Table 6.2: Exercise duration and Borg scores during the control and FWUL tests

Subj.	Test done first	Borg scores*				Exercise duration (minutes)		
		dyspnoea		leg pain				
		C	FWUL	C	FWUL	C	FWUL	Δ%
1	FWUL	4	4	8	8	12.5	14.6	17
2	C	10	9	7	10	17.5	23.6	35
3	FWUL	8	6	8	8	12.9	14.4	12
4	C	7	7	10	10	9.8	8.4	-14
5	C	9	10	10	9	9.8	9.8	1
6	FWUL	3	3	4	4	7.2	9.8	36
7	FWUL	6	5	5	3	10.1	7.5	-26
Mean		7	6	7	7	11.4	12.6	9
SE		1	1	1	1	1.2	2.1	9

C, control test; * Appendix B;
Δ%, difference (FWUL - C) expressed as % control values.

Figure 6.2 illustrates $\dot{V}E$ increasing throughout constant work exercise during both the control and FWUL tests in all subjects. The subject numbers are given in the top left-hand corner of each panel. Note that the subjects tended to achieve high

[1] ATPD, Ambient temperature, pressure and dry conditions

[2] STPD, Standard temperature (273 °K), pressure (760 mmHg) and dry conditions

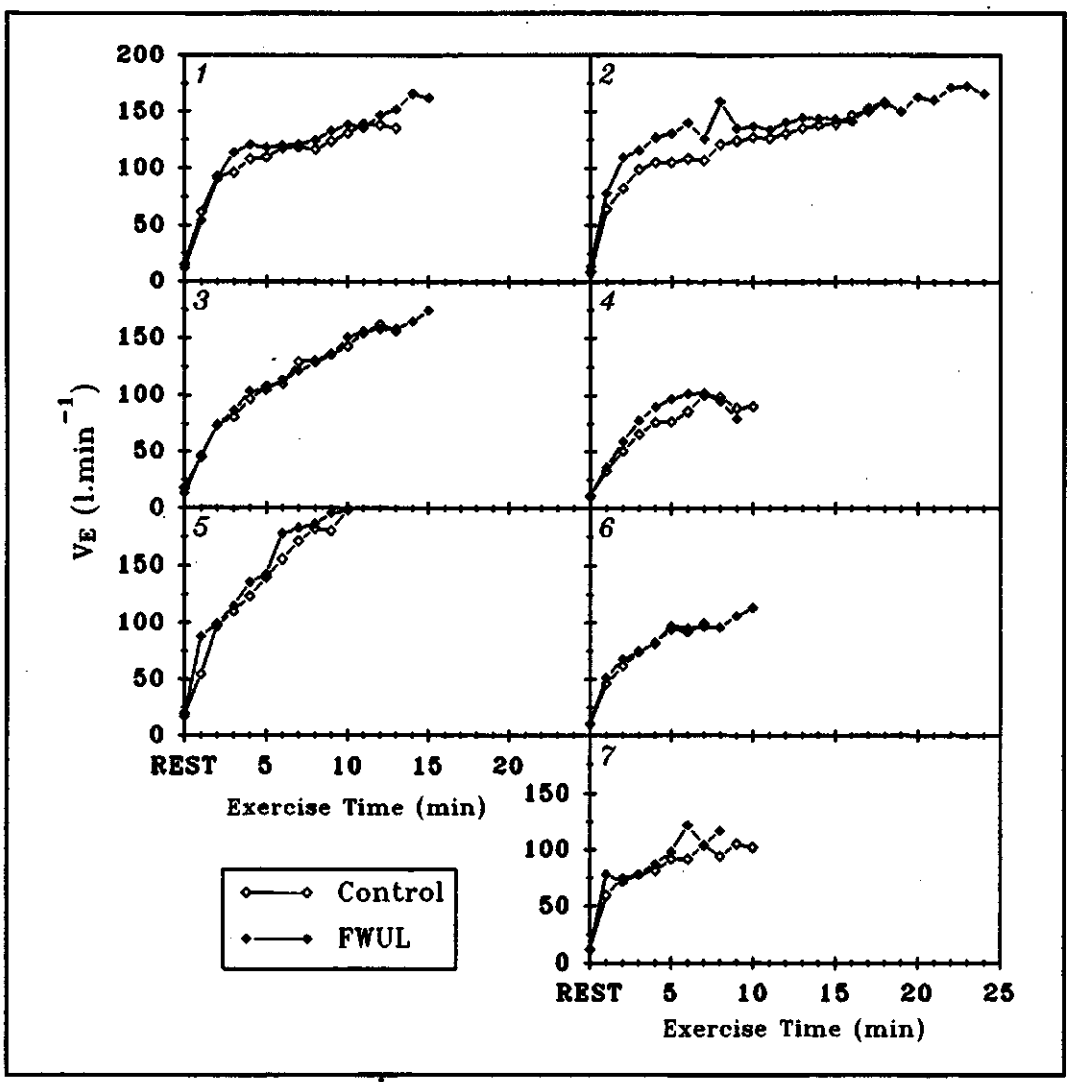

Figure 6.2: Increases in $\dot{V}_E$ during heavy exercise - control and FWUL tests

$\dot{V}_E$ levels early in exercise (2 - 3 minutes). No difference was observed in the ventilatory pattern between the control and FWUL tests. Repeated measures ANOVA (Table 6.3) was used to look for differences in the ventilatory variables between the two tests. The 3 periods of exercise chosen in the control and FWUL tests were: (1) 50% control duration, (2) matched time (the data from the last minute of the shorter test was matched with data at the same time in the other test) and (3) end exercise minute values.

Table 6.3: Results of repeated measures ANOVA[3] - ventilatory variables

Ventilatory variable	50% C-duration		Matched time		End exercise	
	C	FWUL	C	FWUL	C	FWUL
$\dot{V}_E$ ($l \cdot min^{-1}$)	110 (9)	114 (8)	133 (14)	137 (14)	134 (14)	144 (14)
V_T (l)	2.8 (0.1)	3.1 (0.2)	2.6 (0.2)	2.9 (0.2)	2.6 (0.2)	2.8 (0.2)
f (/min)	39 (3)	39 (3)	51 (6)	49 (6)	52 (5)	53 (5)
T_I/T_{TOT}	0.51 (0.09)	0.49 (0.01)	0.51 (0.00)	0.51 (0.00)	0.51 (0.00)	0.52 (0.01)
$\dot{V}O_2$ ($l \cdot min^{-1}$ STPD)	3.33 (0.3)	3.23 (0.2)	3.46 (0.3)	3.29 (0.3)	3.47 (0.3)	3.40 (0.3)
$\dot{V}O_2$ (% peak $\dot{V}O_2$)	88 (3)	86 (3)	92 (5)	86 (4)	92 (6)	89 (4)
HR (bpm)	169 (3)	168 (5)	181 (4)	181 (4)	181 (4)	183 (4)
$PETCO_2$ (mmHg)	36.9 (1.2)	36.4 (1.5)	31.8 (1.6)	32.2 (1.5)	31.4 (1.5)	30.6 (1.2)

All values are mean (n = 7); SE in parentheses; C, control test

There was no significant difference in any of the ventilatory variables between the control and unload tests. The subjects exercised at ~90% of their peak $\dot{V}O_2$ throughout exercise in both tests. The end exercise $\dot{V}O_2$, HR and $PETCO_2$ were similar in both tests indicating that the subjects reached comparable levels of exhaustion on both days. FWUL therefore had no effect on the ventilatory pattern of submaximal heavy exercise.

6.3.2 Changes in Pmus with unloading

Ppl was measured in five subjects throughout exercise on both control and

[3] SPSS-X™, Statistical software, SPSS Inc, Illinois.

unloading days and was used in the calculation of Pmus. The method for calculating Pmus was described earlier (chapter 5). Figure 6.3 shows the average (5 subjects) Pmus during exercise in both tests. Data from two periods (50% control time, matched time) are shown. The average $\dot{V}$, Pm and Ppl are also shown. All waveforms were aligned with the start of inspiratory flow. With unloading average Ppl was less negative during inspiration and less positive in expiration indicating that the subjects exerted smaller intrathoracic pressures to cause airflow. Peak inspiratory

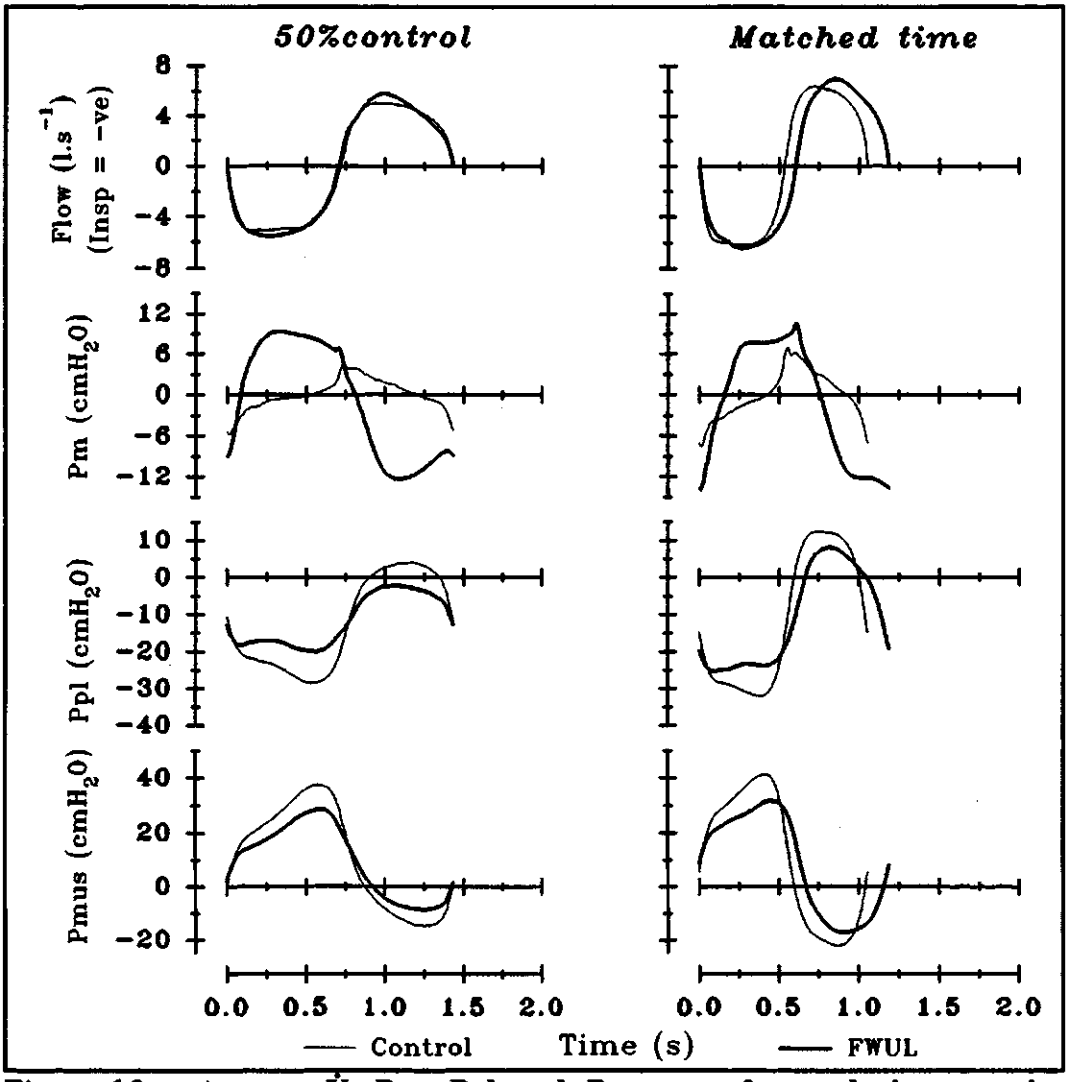

Figure 6.3: Average $\dot{V}$, Pm, Ppl and Pmus waveforms during exercise (control and FWUL) in 5 subjects

and expiratory Pmus were also reduced with FWUL indicating that the respiratory muscles were unloaded. Pmus was calculated for each minute of exercise in the five subjects in whom IC and Ppl were measured, in both tests. Peak inspiratory and expiratory Pmus were significantly less (ΔI - 18%, ΔE - 36%) throughout exercise with unloading. The temporal profile of mean Pmus $\left(\frac{1}{T_{TOT}} \times \int_0^{T_I,T_E} P_{mus}\,(I,E)\right)$ during exercise in the control and FWUL tests is illustrated in figure 6.4. The subject

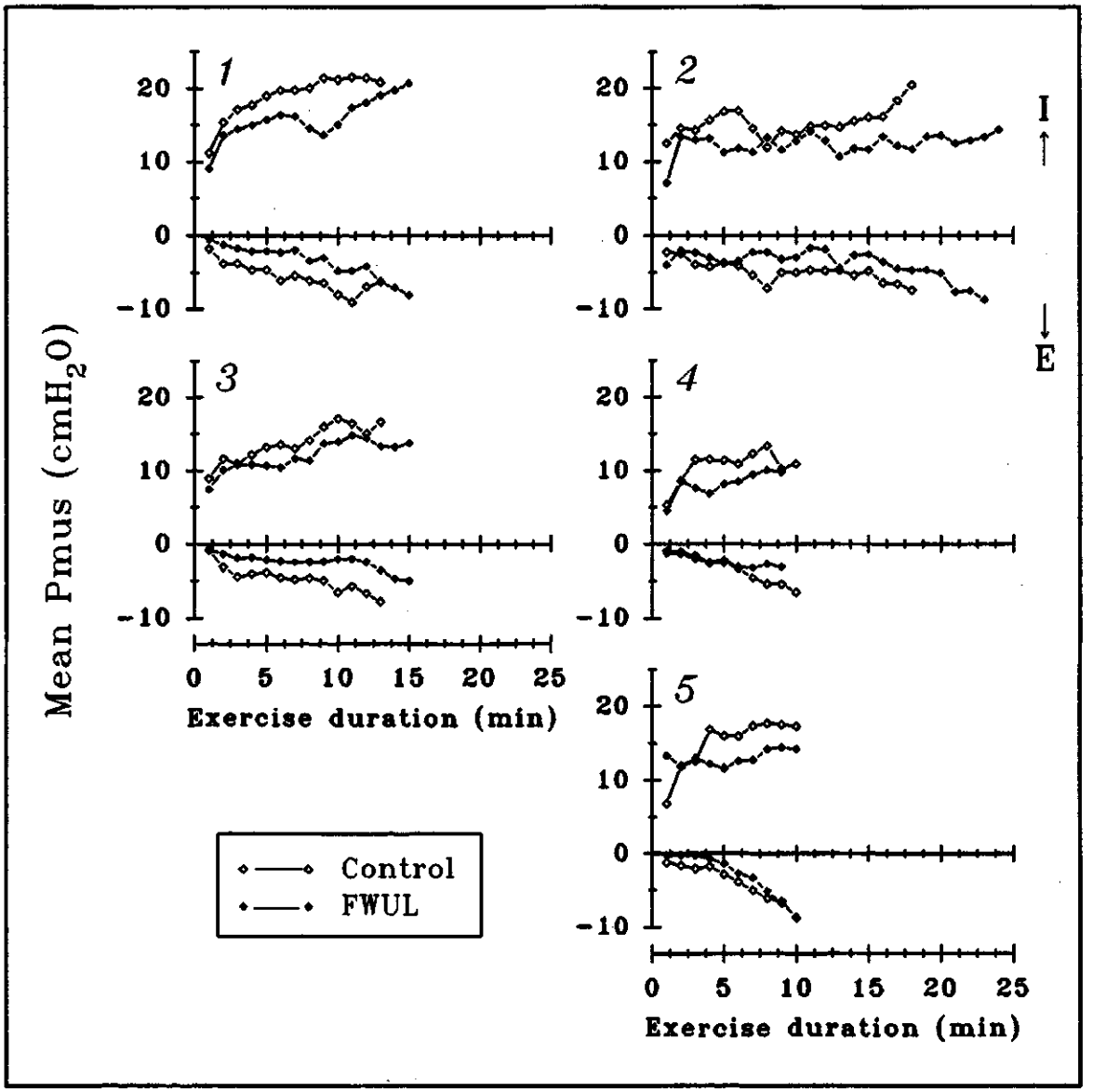

Figure 6.4: Temporal profile of mean Pmus during heavy exercise

numbers (top left) correspond to those in table 6.2. The effects of unloading on respiratory motor output are clearly seen. Mean Pmus(I) throughout exercise was consistently less (mean Δ, 16%) with unloading. Mean Pmus(E) was also less with unloading but was more variable (mean Δ, 37%) among subjects. Total Pmus (Mean I + E), which is the vertical distance between the mean Pmus(I) and Pmus(E) curves, represents the net motor output of the respiratory muscles (I & E). This was also significantly less (mean Δ, 21%) with unloading. Table 6.4 shows the results of repeated measures ANOVA for Pmus variables.

Table 6.4: Results of repeated measures ANOVA[3] - Pmus variables

Pmus (cmH_2O)	50% C-duration			Matched time			End exercise		
	C	FWUL	Δ(%)	C	FWUL	Δ(%)	C	FWUL	Δ(%)
Peak (I)	38.4 (2.5)	29.0** (2.1)	-24 (4)	41.8 (4.0)	33.4* (2.5)	-19 (5)	42.0 (3.8)	35.3* (3.3)	-15 (4)
Mean (I)	15.0 (1.4)	11.9** (1.3)	-21 (3)	16.9 (1.8)	13.6† (1.6)	-18 (6)	17.0 (1.7)	14.6* (1.8)	-14 (4)
Peak (E)	16.1 (1.5)	9.4** (1.0)	-41 (6)	22.7 (1.9)	18.1 (2.8)	-20 (10)	23.8 (1.4)	23.1 (3.0)	-0.4 (16)
Mean (E)	4.2 (0.2)	2.2* (0.3)	-44 (9)	7.0 (0.6)	5.2 (1.0)	-26 (11)	7.2 (0.5)	7.0 (1.3)	-3 (19)
TTmus(I)%	17.8 (1.9)	14.0** (1.5)	-21 (5)	20.0 (2.0)	15.5 (1.6)	-19 (7)	20.2 (2.8)	16.5* (1.9)	-17 (5)
Total Mean (I+E)	19.2 (1.8)	14.1** (1.3)	-26 (2)	23.9 (2.1)	18.9* (2.3)	-21 (6)	24.3 (1.8)	21.6 (2.7)	-13 (6)

All values are mean (n = 5); SE in parentheses; C, control test;
Δ(%), difference (FWUL - C) as % control values;
*, statistically different from control values ($p < 0.05$); †, $p = 0.057$
**, statistically different from control values ($p < 0.01$);

6.4 Respiratory muscles and endurance exercise performance

The objective of this study was to explore the possibility that the respiratory system could contribute directly to the limitation of endurance exercise. Most of the evidence that suggest this possibility have looked at respiratory muscle function

during maximal incremental exercise [Younes and Kivinen, 1984] or at the end of sub maximal exercise [Bye *et al*, 1976]. Respiratory muscle function throughout constant work-rate heavy exercise is quite different from incremental exercise as high $\dot{V}_E$ levels are reached earlier in the former. If the high ventilatory load on the respiratory muscles throughout endurance exercise contributed to exercise limitation, reducing part of the load (FWUL) throughout exercise should improve exercise performance.

No significant difference in the ventilatory or exercise variables was found in this study. In addition, FWUL did not improve (increase duration) endurance exercise performance. Although the subjects were exercising at levels that represented ~90% of their $\dot{V}O_2max$, there was considerable variation in exercise tolerance among subjects. Statistical analysis revealed that given the variability in exercise performance among the subjects, the chance of missing a 25% increase in exercise duration with FWUL was less than 15% (Type II error = 0.15, [Freiman *et al*, 1978]). The possible reasons for the lack of any improvement in exercise duration are: (1) the reduction in respiratory muscle load (73% of airflow resistance) was not sufficient to produce any significant reduction in respiratory muscle work, (2) the respiratory muscles were not contracting at fatiguing levels for the unloading to make any difference in exercise ventilation.

Many attempts have been made to examine the phenomenon of respiratory muscle fatigue during heavy exercise. Some of the direct and indirect evidences suggesting the possibility of respiratory muscle fatigue occurring during heavy exercise had been reviewed in chapter 2. It has been shown that the inspiratory muscles are operating near or above fatiguing levels at the end of exhausting (incremental)

exercise [Younes and Kivinen, 1984]. The mean muscle pressures measured at end exercise have been found to exceed the critical threshold that is associated with the development of fatigue. A measure of how close to this threshold the subjects (five) in this study were, was assessed. The tension· time index [Bellemare and Grassino, 1982] for the inspiratory muscles $\left(TT_{mus}(I) = \frac{1}{T_{TOT}} \int_0^{T_I} \frac{P_{mus}(I)}{P_{STR}(I)} \right)$, defines this critical threshold. $P_{STR}(I)$ is the maximum negative pressure (less the elastic pressure loss of the chest wall) that can be generated at any given lung volume and was measured in five subjects (see chapter 5). $TT_{mus}(I)$ was thus estimated throughout exercise from the calculated $P_{mus}(I)$ and the measured $P_{STR}(I)$ values in both the FWUL and control tests.

There is a strong relationship between $TT_{mus}(I)$ and the onset of fatiguing contractions in inspiratory muscles. It has been shown that diaphragmatic contractions could be maintained indefinitely when the index was less than 0.15 [Bellemare and Grassino, 1982]. These authors also demonstrated that when the index was > 0.15 the duration of fatiguing contractions (TLIM) was a power function of $TT_{mus}(I)$ ($TLIM = 0.1 \cdot TT_{mus}(I)^{-3.6}$). In the present study it was found that the $TT_{mus}(I)$ with FWUL was less than control throughout exercise (Table 6.3). This fall (18%, throughout exercise) in $TT_{mus}(I)$ with unloading should have resulted in a doubling of inspiratory muscle contraction time. As table 6.4 shows, the subjects exercised at or above fatiguing levels of inspiratory muscle contraction throughout exercise, during the control test. The fact that the subjects exercised at these fatiguing levels and the lack of any improvement in exercise tolerance with resistive

unloading, indicates that respiratory muscle fatigue does not contribute to exercise limitation in normal healthy humans. The lack of any significant difference in ventilatory variables ($\dot{V}E$, VT, *f*) or exercise parameters (HR and $\dot{V}O_2$) along with a significant fall in neuromuscular output with unloading suggests that during prolonged exercise, the respiratory controller responds to the applied assist with a reduced mechanical output to maintain ventilation.

6.5 Summary

An unloading device and its accessories was modified in order to apply full wave resistive unloading throughout heavy exercise in seven normal subjects. An attempt was made to see if reducing the loads on the respiratory muscles during heavy exercise improved exercise duration. The results of the study showed that the respiratory muscles are contracting at or above potentially fatiguing levels throughout prolonged exercise. Unloading of the respiratory muscles caused a significant reduction in muscle pressures for a given ventilatory need, but did not increase exercise duration. The fall in inspiratory muscle pressures with the significant reduction in the $TT_{mus}(I)$ throughout exercise with unloading predicted a doubling of inspiratory muscle endurance. However, respiratory muscle unloading throughout endurance exercise did not improve exercise tolerance. The data also suggest that during heavy exercise although respiratory muscle fatigue may occur, it does not play a significant role in exercise limitation in normal healthy subjects.

7. SUMMARY AND CONCLUSIONS

Alteration of the mechanical load on the respiratory system has been a useful technique to explore the normal behaviour of the respiratory pump. Loading the respiratory muscles both at rest and during exercise has provided valuable information about normal respiratory mechanics and the extent of interaction between mechanical and chemical factors in the control of exercise ventilation. The ventilatory responses to loading depend on the type and severity of the load and are different between rest and exercise. The response during exercise seems to be the result of a compromise between mechanical adjustments in the respiratory pump and the maintenance of gas exchange equilibrium.

Reduction of the load on the respiratory pump (unloading) also has provided information on the influence of respiratory mechanical factors on exercise ventilation. He-O_2 (low density) mixtures have long been used with exercise to effect resistive unloading. The effects of He-O_2 are predominantly during moderate to heavy exercise when it reduces turbulence in major airways, thus reducing resistance. The degree of unloading provided by He-O_2 is variable throughout the airways (turbulent flow occurs usually only in larger airways). Furthermore He-O_2 reduces only that part of the total resistance which is associated with turbulent flow in the airways.

A variety of mechanical devices have been used in the past to alter the load on the respiratory system. Some of these have been used in respiratory muscle unloading during exercise with limited success. A recently developed loading/unloading device (described in chapter 4) was a significant improvement over

conventional pressure assist ventilators. The main objective of this project was to modify this device and its accessories to provide proportional respiratory muscle unloading throughout constant load heavy exercise in moderately fit subjects. Pilot studies with the prototype of this device revealed a number of modifications that were necessary to make the device operational with heavy exercise. The device was successfully modified to provide proportional respiratory muscle unloading, with the high ventilatory levels of heavy exercise.

It has been questioned whether the normally present loads in the respiratory system contribute directly or indirectly to the cessation of prolonged exercise in normal humans. The occurrence of respiratory muscle fatigue during exercise has been investigated. Some studies have revealed that the inspiratory muscles could be contracting at or above potentially fatiguing levels at the end of incremental exercise. Fatigue, if it occurs, is a cumulative process throughout exercise. The hypothesis tested in this study is that the normal respiratory load (with or without respiratory muscle fatigue) contributes to the limitation of prolonged exercise in normal humans, not that it is the sole limiting factor. If respiratory loads contribute to limitation then reducing the resistive loads against which the respiratory muscles operate during constant load heavy exercise should enhance performance. A study was designed to test the above hypothesis in seven, fit, male subjects. The unloading device was successfully used to apply full wave (I and E) resistive unloading that was proportional to the subjects' measured intrinsic resistance (~73%). The subjects performed constant load heavy exercise (@ ~90% peak $\dot{V}O_2$) on two different days. On one day the unloading device applied a mouth pressure proportional to flow

resulting in unloading. In order to ascertain whether the respiratory muscles were actually unloaded intrathoracic pressures were measured in five subjects. Chest wall recoil pressure and maximum (negative) pressure capacity of the inspiratory muscles had also been previously assessed in these subjects. The results of the study revealed no difference in either the ventilatory or exercise performance in all subjects between the control and unload days. In addition, respiratory muscle unloading throughout exercise did not improve endurance exercise duration.

Respiratory muscle output (P_{mus}) was calculated for each minute of exercise on both control and unload days in the subjects in whom Ppl was measured. The mean values of both Ppl and P_{mus} were significantly lower with unloading indicating the respiratory muscles had been unloaded. To examine whether the inspiratory muscles were contracting at fatiguing levels, tension-time (TT) index was measured for each minute of exercise during both tests. TT is an index which estimates fatiguability of the muscles using a ratio of output to capacity. A value of 0.15 has been estimated as the level at which the diaphragm can contract indefinitely. Calculation of TT $P_{mus}(I)$ showed that the inspiratory muscles were contracting at or above potentially fatiguing levels (TT > 0.15) throughout exercise during the control test. TT of the inspiratory muscles was however significantly lower throughout exercise with unloading. The absence of any difference in either the exercise or the ventilatory variables between control and unloading associated with reduced neuromuscular output with FWUL indicates that the normal ventilatory load does not constrain prolonged exercise.

Resistive loads make up only a part ($\sim$35%) of the total mechanical loads in

the respiratory system. Approximately 73% of this resistance was unloaded in this study. It is arguable that this reduction was not significant enough to produce any perceptible change in exercise performance. It has been shown that for the inspiratory muscles there is a strong relationship between contraction endurance time and TT. The demonstrated reduction of load on the inspiratory muscles throughout exercise with a reduced TT in this study, should have at least doubled contraction endurance time for the inspiratory muscles. Although unloading reduced inspiratory muscle work significantly, endurance exercise performance was not improved. Statistical analysis indicates that the chance of missing a small but significant improvement in exercise duration in this study, is less than 15%. It is therefore concluded that the resistive load on the respiratory muscles does not contribute to endurance exercise limitation in normal humans.

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APPENDIX A

EXERCISE TEST QUESTIONNAIRE

Name - _____ **Age** - _____ **Sex** - M/F

Height - _____ in/cm **Weight** - _____ lbs/kgs

Race - _____ (Caucasian, Sask. Native, Asian)

Home address - _____

_____

Telephone - (Off) _____ (Res) _____

1.	Have you ever had chest pain ?	YES | NO
2.	Have you ever had tightness in your chest ?	YES | NO
3.	Do you have shortness of breath for normal activity ?	YES | NO
4.	Do you have high blood pressure ?	YES | NO
5.	Do you ever wheeze or have asthma ?	YES | NO
6.	Have you ever had palpitations ?	YES | NO
7.	Do you have a heart 'murmur' ?	YES | NO
8.	Do you have an 'irregular' pulse ?	YES | NO
9.	Have you had a 'cold' or 'flu' in the last month ?	YES | NO
10.	Do you currently smoke ?	YES | NO
11.	Have you ever smoked ?	YES | NO
	If **Yes**, How many years ? _____ yrs	
	Number _____ /day	
	stopped smoking for _____ yrs/mths	
12.	Do you exercise regularly ?	YES | NO
	If **Yes**, Type of exercise _____	
	_____ times/week	
	Length of session _____ Hrs/min	
13.	Have you ever had:	
	Any diseases of the lung ?	YES | NO
	Any diseases of the heart ?	YES | NO
	Medications in the last three months ?	YES | NO
	If **Yes**, What are you taking ? _____	
	What condition ? _____ for _____ mths	

APPENDIX B

Modified Borg scale of perceived exertion

0	Nothing at all
0.5	Very, Very mild (just noticeable)
1	Very mild
2	Mild (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (almost max.)