THE ROLE OF EXPIRATORY MUSCLE ACTIVITY
IN
VENTILATION DURING EXERCISE

By

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ABSTRACT

The quantitative importance of expiratory muscle activity in breathing at rest and during exercise remains uncertain. While the expiratory muscles are relatively inactive at rest, their activity increases substantially during exercise. In recent years, the role of expiratory muscles in decreasing end-expiratory lung volume, thereby optimizing inspiratory muscle activity has overshadowed their contribution to increasing expiratory flow. No information is available in the literature on the partitioning of the work of breathing performed in increasing expiratory flow or decreasing expiratory lung volume during exercise. Neither has the interaction between the work performed by expiratory muscle with that performed by inspiratory muscle during exercise been investigated. The purpose of this thesis is to investigate the partitioning of work performed by the expiratory muscles between controlling operating lung volume and increasing expiratory flow, as well as the importance of the expiratory work in determining maximal ventilation during exercise.

Healthy subjects were studied at rest and six levels of exercise, including maximum exercise (WR_{max}). Esophageal and gastric pressure (P_{es} and P_{ga}) were measured using standard balloon catheter systems. Lung volume was measured using inductance plethysmography, calibrated at each exercise work rate with inert gas dilution and spirometric volumes. The static effects of lung and chest wall recoil on esophageal pressure ($P_{es\text{-}stat}$ and $P_{el,w}$ respectively) were measured at rest ($P_{el,w}$ was estimated for some subjects). Work of breathing was measured for both inspiratory and expiratory muscle activity and further partitioned into elastic and resistive work. Measures were made when subjects breathed through a mouthpiece and during free breathing.

During the transition from rest to mild exercise (50W), end-expiratory lung volume fell from 53.0 ± 3.7 to 47.6 ± 3.6 (M ± SE) percent of total lung capacity, there was a further significant decrease with 100W exercise to 44.0 ± 3.8 %TLC, at maximal exercise, end-expiratory volume was 40.3 ± 2.5 %TLC. There were no differences between EELV responses under on and off-mouthpiece conditions.

During exercise, expiratory flow was greater than that which could be achieved passively (i.e. due to the combined elastic recoil of the lung and chest wall). At maximal exercise, approximately half of the measured expiratory flow was due to expiratory muscle activity. The extent to which expiratory flow was dependent on expiratory muscle activity was greatest at low lung volumes, where the combined elastic recoil of the lung and chest wall was relatively small.

Expiratory esophageal pressure progressively increased during the course of exercise. This increase in pressure was associated with significant increases in expiratory flow at all work rates, including maximal exercise. Expiratory pressure remained effective throughout the majority of expiration (i.e. it did not exceed the point at which starling type resistance prevents further increases in expiratory flow). Transient ineffective pressure toward end expiration may have occurred during maximal exercise.

The total work of breathing at a given level of ventilation was in agreement with studies reported in the literature. At rest all work was performed by inspiratory muscles. During mild exercise (50W), expiratory muscle work was significant, accounting for 10.5 ± 2.1 % of the total work of breathing ($p<0.05$). This percentage increased with exercise work rate and during maximal exercise it reached 26.6 ± 2.9 ($p<0.05$).

During mild to moderate exercise (50 - 150W) the expiratory work used to lower end-expiratory volume below functional residual capacity exceeded that used for increasing expiratory flow ($p<0.05$). At maximal exercise however, the work performed increasing expiratory flow accounted for 71 ± 9.2% of the total expiratory work and was significantly greater than the work used to lower end-expiratory volume ($p<0.05$).

Ventilation during maximal exercise could not be achieved without expiratory muscle activity, illustrating the importance of these muscles in lowering end-expiratory lung volume and increasing expiratory flow.

This study for the first time has quantitatively established the importance of expiratory muscle activity during exercise, and shown that the developed power is used for regulating operating lung volume, and increasing expiratory flow.

ACKNOWLEDGEMENTS

With the completion of this work, I have a sense of personal accomplishment, and at the same time a considerable feeling of indebtedness to the people who have provided help and guidance along the way. It is a pleasure to acknowledge them here.

Six years ago I had an idea that expiratory muscles did more during exercise than textbooks said they did. When I approached Kieran Killian about the possibility of his supervising my PhD on this topic, he sat me down and talked *at* me for what seemed an eternity. One of my major achievements is that I can now on occasion talk *with* Kieran. Thank-you Kieran, for letting me do what I wanted, and for demanding by example, that I understood what it was I'd done.

When I first started this project, I understood nothing about respiratory mechanics. I would like to thank Moran Campbell for realizing this within five minutes of beginning our first discussion and checking throughout the next six years that I was actually doing something about it.

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James Nicholas Inman wasn't born when I started this, now he's nearly three. Thank-you James, for breathing and, for not caring how.

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TABLE OF CONTENTS

FIGURES

TABLES

ABBREVIATIONS

A/D	analogue to digital conversion
$ANOVA_{rm}$	repeated measures analysis of variance
BTPS	body temperature and pressure saturated
d	displacement
E	elastance
E_w	chest wall elastance
E_L	lung elastance
E_{rs}	respiratory system elastance
EELV	end-expiratory lung volume
EILV	end-inspiratory lung volume
EMG	electromyography
F	force
F_{CO2}	carbon dioxide fraction
F_{He}	helium fraction
F_{O2}	oxygen fraction
f	frequency
f_n	natural frequency
FRC	functional residual capacity
I	inertia
I_{rs}	respiratory system inertia
K	spring constant
M	mass
max-dyn	maximum dynamic inspiratory and expiratory effort
MEP	maximum expiratory pressure
MEP_{dyn}	MEP under dynamic conditions
MEP_{stat}	MEP under static conditions
MIP	maximal inspiratory pressure
MIP_{dyn}	MIP under dynamic conditions
MIP_{stat}	MIP under static conditions
off-mp	off-mouthpiece
on-mp	on-mouthpiece
P	pressure
P_A	alveolar pressure
P_{ab}	abdominal pressure
$P_{el,w}$	pressure from chest wall elastic recoil
P_{es}	esophageal pressure
$P_{es\text{-}stat}$	esophageal index of $P_{pl\text{-}stat}$
P_{ee}	end-expiratory esophageal pressure
P_{ei}	end-inspiratory esophageal pressure
P_{ET}	extrathoracic pressure
P_{ga}	gastric pressure
$P_{el,L}$	pressure from lung elastic recoil
P_m	mouth pressure

P_{maxeff}	maximum effective pressure
P_{mus}	pressure from muscle contraction
P_{pl}	pleural pressure
$P_{pl\text{-}stat}$	pleural pressure to overcome static lung recoil
$P_{el,rs}$	pressure from respiratory system elasic recoil
R	resistance
R_{airway}	airway resistance
R_w	chest wall resistance
R_L	lung resistance
R_{pulm}	pulmonary resistance
R_{rs}	respiratory system resistance
RER	respiratory exchange rate ($\dot{V}_{O2}/\dot{V}_{CO2}$)
RV	residual volume of lung
TLC	total lung capacity
$T_{exhaust}$	time to exhaustion in protocol 2 test
T_r	room temperature
V	volume
V_L	lung volume
V_{spir}	gas volume of spirometer
V_T	tidal volume
$\dot{V}$	volume rate of change
$\dot{V}_E$	minute ventilation
$\dot{V}_{exp}$	expiratory flow rate
$\dot{V}_L$	rate of lung volume change
$\dot{V}_{insp}$	inspiratory flow rate
$\ddot{V}$	$\dot{V}$ rate of change
VC	vital capacity
W	work
W_{insp}	work of inspiration
W_{exp}	work of expiration
$\dot{W}$	rate of work (power)
WR	exercise work rate
WR_{max}	maximum exercise work rate
WR_{mx-1}	measures made 1 min prior to exhaustion at WR_{max}

INTRODUCTION

Muscular work is required to inflate the lung during inspiration. Expiration at rest does not involve muscular activity but depends on elastic energy stored during inspiration. However, during exercise the muscles of expiration are active. Regulation of operating lung volume, thereby lengthening and assisting inspiratory muscle activity, and the generation of expiratory flow are the effects most often presumed to result from expiratory muscle activity. The purpose of this thesis is to quantify the work performed by expiratory muscle in achieving these effects and to examine the interacting roles of inspiratory and expiratory muscle activity during exercise.

MECHANICS OF BREATHING

HISTORICAL ASPECTS

Galen was aware in the second century that the lungs are inflated as a result of expansion of the chest wall:

> "the whole thorax expands in inspiration.....and causes the entire lung to fill the space left vacant".

This was based on observations of damage to the nerve supply of the diaphragm, or to the intercostal muscle of the rib cage resulting in difficulty or cessation of breathing.

The dependence of lung volume on motion of the chest wall was not illustrated until the sixteenth century by Vesalius (Foster, 1901), who observed the lungs collapse when the thorax of dogs were opened. He also observed the simultaneous motion of the lung and diaphragm in dogs in which the tissue overlying the pleura had been removed.

While it was known that the lungs moved because the chest wall moved, the pressure changes responsible for this motion were not known. Descartes ((1662) cf (Otis, 1964)) suggested that the movement of the thorax resulted in the compression of adjacent air and created a series of compression waves, so that the pressure at the mouth became elevated, forcing air into the lungs in the same manner as air is forced into an elastic balloon.

Mayow (1674) was the first to suggest that atmospheric pressure was responsible for lung inflation and that a gradient was created by lowering the pressure in the space surrounding the lung. He proposed a model of the respiratory system based on a bladder contained within a bellows, with the mouth of the bladder sealed to the mouth of the bellows. Mayow suggested that muscle contraction resulted in outward motion of the chest wall (analogous to expansion of the bellows), lowering the pressure surrounding the lung (bladder) and resulting in inflation. He further suggested that expiration was passive:

> "...in expiration the parts of the thorax return by a movement of restitution to their natural position, without any aid from the muscles."

The mechanism of air entry proposed by Mayow was described in more detail by von Haller (1803):

> "...the cavity of the breast, which is filled by the lungs be dilated. The air which is in the lungs expands into this increased space, by which, being weakened in its spring, it makes decreased resistance to the external air; consequently a portion of the external air descends into the lungs, sufficient to restore the air now contained in the lungs, the same density with that of the external air"

While von Haller was aware that at rest, expiration was passive and occurred "more easily" than inspiration, due to the elastic recoil of the "ribs and lung itself", he suggested that during increased ventilation, muscle activity was responsible for some of expiration:

> "In violent respiration.....the more powerful expirations derive assistance from some other causes."

At this stage, investigators were aware that the tendency of the lung to collapse is prevented by the negative pressure in the pleural space. Inspiration was thought to occur through muscle activity, expanding the chest wall, further lowering the pleural pressure and thus expanding the lung. Expiration was believed to be passive, due to recoil of the lung and chest wall, although contribution from muscle activity with increased ventilation was noted. Quantitative understanding was made possible with the advent of several measurement techniques:

Lung Volume: Hutchinson (1844) used a water filled spirometer to measure the vital capacity (maximum volume of air that could be expired following a maximal inspiration). The use of a tracer gas (hydrogen) was first employed by Davy to measure absolute lung volume (Otis, 1964).

Recoil Pressures: The first time the recoil pressure of the lungs was measured was by Carson ((1820) cf (Otis, 1964)), who attached a water manometer to the airways of several animal species and observed the recoil pressure when the chest was opened. This procedure was used by Donders (1853) to measure the recoil pressure of the lungs in recently deceased human cadavers. He observed recoil pressures ranging from 3 to 7 cmH_2O. Donders (1853) observed greater recoil pressures if a volume of air was forced into the lungs prior to the opening of the chest, illustrating that the elastic recoil of the lungs is dependent on lung volume.

Bernoulli ((1911) cf (Otis, 1964)) measured the recoil pressure at the mouth in relaxed human subjects at several lung volumes, establishing a pressure volume relationship for the respiratory system. However, relating the recoil pressure of the lung to the lung volume was more difficult, as any measures made at the mouth, reflect the recoil of the lung, as well as the chest wall. Heysnius ((1882) cf

(Wirz, 1923)) attempted to resolve this issue by measuring the negative pressure applied to the outer surface of excised dog lungs to produce changes in lung volume. He reasoned that the pressures reflected the pleural pressure required to inflate the lung to a similar volume *in vivo*.

Pleural Pressure: The first attempts to measure the pleural pressure required to overcome lung recoil were made by Ludwig ((1847) cf (Wirz, 1923)). Ludwig used a water filled bladder inserted between the parietal and visceral pleura. Apparently the inertia of this device was such that pressure changes could only be observed during major respiratory movements. Wirz (1923) refined this technique and was able to simultaneously measure rabbit pleural pressure and lung volume. As predicted by von Haller, pleural pressure was negative at static volumes, to overcome the elastic recoil of the lung and that during inspiration the pressure became more negative, by an amount proportional to the flow rate. Expiration occurred when pleural pressure increased, and was no longer sufficient to overcome the recoil of the lung.

The concepts developed by these researchers, as well as their measurement techniques form the basis of the current understanding of respiratory mechanics. Mechanical analysis of the respiratory system is complex. The following sections introduce the basic mechanical concepts that are used in the thesis.

EQUATION OF MOTION

The equation of motion formulated by Newton in the seventeenth century describes the motion of a mechanical system that is free to move in a single direction (see fig 1):

$$F = K \cdot x + R \cdot (dx/dt) + M \cdot (d^2x/dt^2) \qquad (1)$$

where F is the force applied to an object of mass M, which is attached to a spring with a spring constant K, and resting on a surface with which the coefficient of friction is R, resulting in movement in direction x, with velocity dx/dt and acceleration d^2x/dt^2.

As first proposed by Descartes ((1662) cf (Otis, 1964)), the laws governing the universe apply to all matter, including living matter. Thus, the equation of motion above could be used to describe the motion of the respiratory system, as a result of forces generated by respiratory muscles. This would however be an almost impossible task, as the respiratory system is complex, with forces and motion occurring in an infinite number of directions. Mechanical assessment of the respiratory system is greatly simplified if pressures are analyzed, rather than forces.

In fig 2, an equation of motion analogous to equation (1) is developed to illustrate the components of pressure required to inflate an elastic balloon. Panel A illustrates the pressure (P) required to overcome the elastic properties of a balloon under static conditions (ie. when the volume of the balloon is not changing). The graph in panel A indicates that as the pressure in a balloon is increased, there is a linear increase in balloon volume (V). Elastance (E) is defined as the inverse slope of this relationship, resulting in the equation:

$$P = E \cdot V \tag{2}$$

Panel B of fig 2 illustrates the pressure required to inflate the elastic balloon under dynamic conditions, when that pressure is applied through a tube offering resistance (R). In this example, the mass of the balloon and air are considered negligible. The pressure required to inflate the balloon under dynamic conditions is shown by the solid curve on the graph in panel B. Also included on this graph is a dashed line, representing the pressure to maintain a static balloon volume (identical to the graph in panel A). The total pressure required to overcome the resistance of the balloon is determined by the resistance (R) and the flow rate ($\dot{V}$), and is illustrated in panel B as the difference between the dynamic (solid) and static (dashed) lines. During the initial period of inflation, the difference between these curves increases, reflecting conditions of increasing flow. During the later stages the difference decreases, reflecting decreasing flow. During the middle stage, the difference is constant, reflecting constant flow. The total resistive pressure is given by the second term in the equation in panel B:

$$P = R \cdot \dot{V} \tag{3}$$

The conditions in panel C of fig 2 are the same as in panel B, except that the mass of the balloon and air (M) are no longer negligible, and a component of the applied pressure must overcome the inertia of the balloon. The solid curve on the graph in panel C illustrates the inflation of the balloon under these conditions. The dashed curve illustrates the inflation of the balloon with negligible mass (identical to the solid curve in panel B). The magnitude of pressure required to overcome inertia is proportional to the mass of the balloon system (M) and the rate of change of flow rate ($\ddot{V}$), and is illustrated as the difference between the solid and dashed curves in panel C. In the early stage of inflation, when the flow rate is increasing, the pressure required to inflate the balloon at a given volume is greater than when mass was negligible. This increased pressure is required to overcome the inertia of the balloon and air. During the middle stage of inflation, where the flow rate is constant, the mass of the balloon and air do not affect the pressure required for inflation. During the later stage, when the flow rate is decreasing, the pressure required to inflate the balloon is less than when mass was negligible. This decreased pressure can be accounted for by the kinetic energy stored in the balloon and air mass, performing some of the work of inflating the balloon. The pressure required to accelerate and therefore overcome the inertia of the balloon and air mass is given in the third term of the equation in panel C:

$$P = M\cdot\ddot{V} \tag{4}$$

The whole equation describing the motion of the balloon system:

$$P = E\cdot V + R\cdot\dot{V} + M\cdot\ddot{V} \tag{5}$$

is analogous to equation (1) but in this form can be used to describe the motion of three dimensional structures such as the respiratory system.

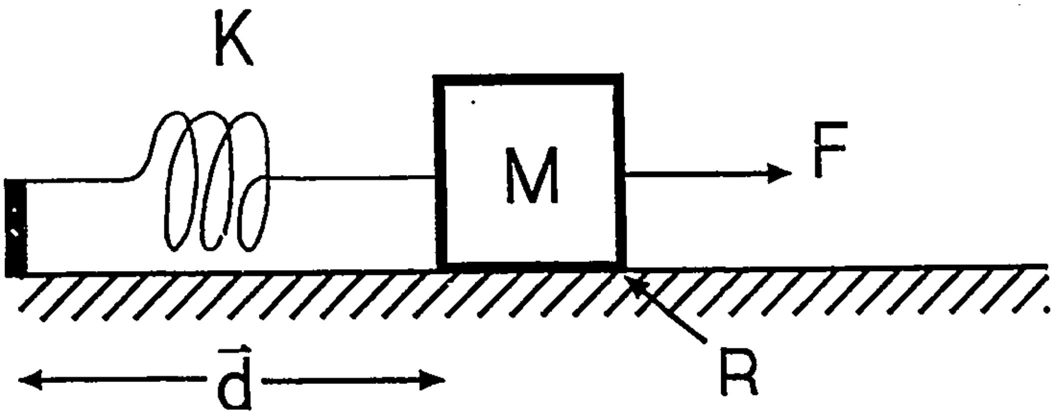


Fig 1 Model of a mechanical system free to move in a single direction. Motion in this system occurs as a result of applied force F, and produces displacement $\vec{d}$. Impedance to motion in this system includes elastance (determined by spring constant K), resistance (determined by the coefficient of friction R) and inertance (determined by the mass of the object M).

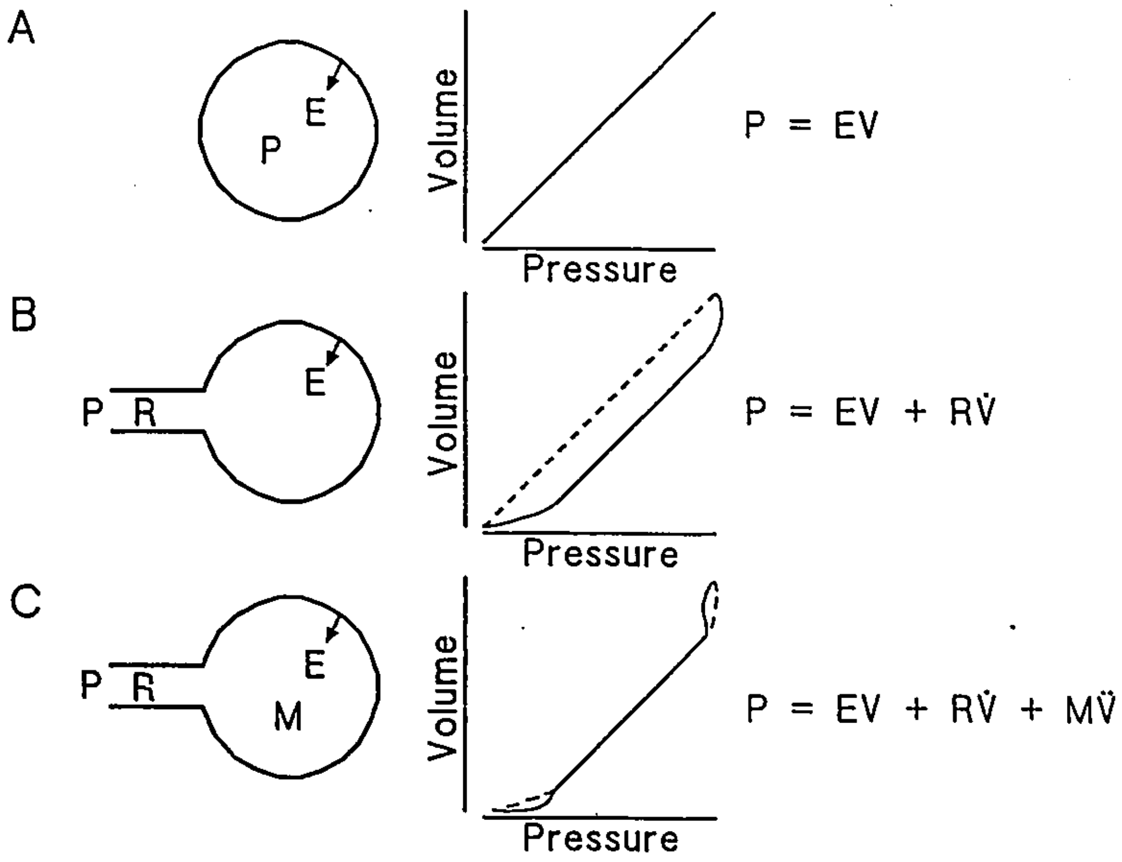


Fig 2 Illustration of the components of pressure required to inflate an elastic balloon. Included are plots of pressure required to overcome elastance (E), resistance (R) and inertance (proportional to mass (M)). Also included is the equation of motion describing the inflation of the balloon.

WORK

In the previous section two forms of the equation of motion were presented, equation (1), describing motion of a system free to move in a single direction (fig 1), and equation (5) which may be applied to a three dimensional system where motion may occur as a result of pressure changes (fig 2). The work (W) performed on the system in fig 1 is given by the equation:

$$W = F \cdot \vec{d} \tag{6}$$

where F is the applied force and $\vec{d}$ is the resulting displacement. The analogous equation for the three dimensional system in fig 2 is:

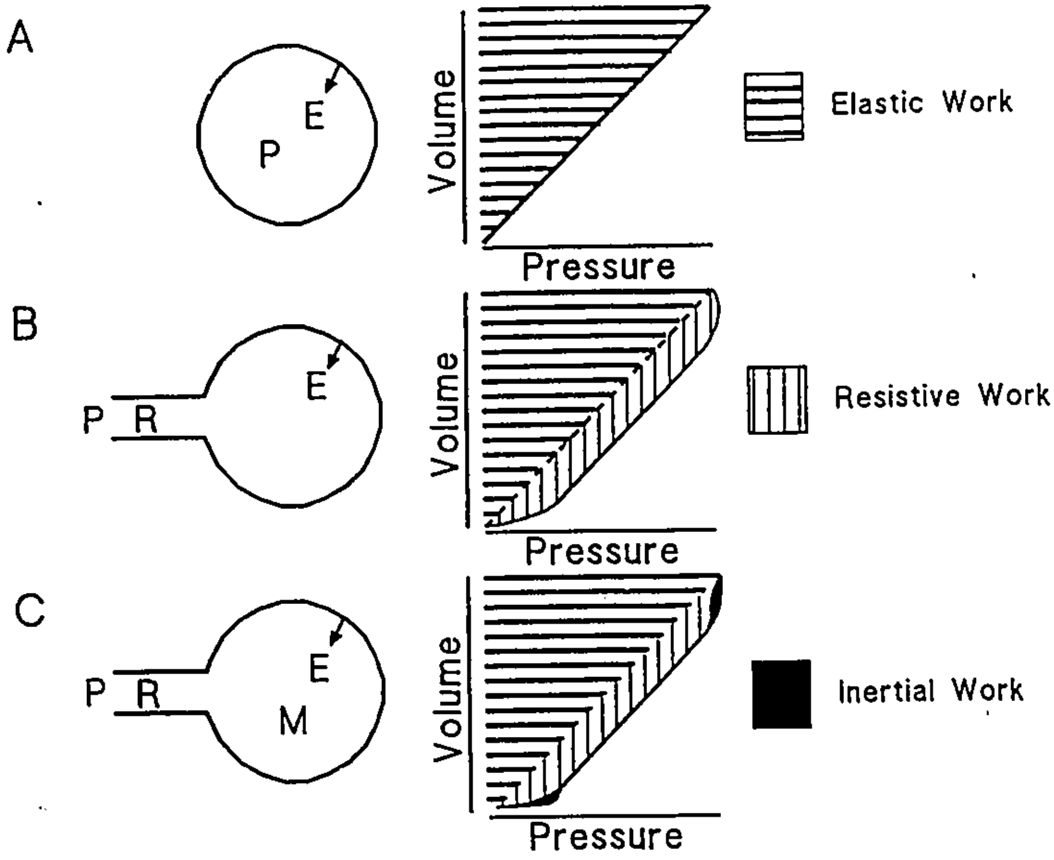
$$W = P \cdot \Delta V \tag{7}$$

where P is the pressure applied resulting in a volume change of ΔV. Thus, the work performed inflating an elastic balloon may be calculated as the area to the left of the curves in fig 2. This work is illustrated in fig 3.

In panel A of fig 3, the shaded area represents the elastic work performed inflating the balloon. This work would not be influenced by the rate at which the balloon was inflated.

In panel B, the resistive work has also been graphed. As the pressure required to overcome resistance is proportional to the flow rate, the resistive work will be proportional to the rate the balloon is inflated.

In panel C, the inertial work has been included. In the early phase of inflation, when the flow rate is increasing, the solid black area represents inertial work performed by the pressure source (P) to accelerate the balloon mass. In the later phase, when the flow rate is decreasing, the solid black area represents work performed by the kinetic energy of the balloon mass. This work is used to overcome the impedance to further inflation. Thus, the initial inertial work is performed on the balloon system, while the later is performed by the system. The total work in each of these phases is equal, and thus there is no net inertial work performed on the system during inflation.



<u>Fig 3</u> Illustration of the components of work performed to inflate an elastic balloon. Shaded areas represent the amount of work performed overcoming elastance (elastic work), resistance (resistive work) and inertance (inertial work).

MECHANICAL MODEL OF RESPIRATORY SYSTEM

A model of the respiratory system based on the above concepts is presented in fig 4. In this model, the respiratory system is divided into pleural and abdominal cavities, separated by the diaphragm. Contained within the pleural cavity is the lung, represented by a balloon. The pressures that must be considered when analyzing the motion of the respiratory system are illustrated on the figure. The relationships between these pressures, responsible for motion are:

1/ Flow ($\dot{V}$) occurs into or out of the lung at a rate dependent on the difference between alveolar pressure (P_A) and mouth pressure (P_m) and the airway resistance (R_{airway}):

$$\dot{V} = \frac{P_A - P_m}{R_{airway}} \tag{8}$$

2/ Alveolar pressure is dependent on the extent to which lung elastic recoil pressure ($P_{el,L}$) is balanced by pleural pressure (P_{pl}):

$$P_A = P_{el,L} + P_{pl} \tag{9}$$

3/ Pleural pressure is balanced by the elastic recoil pressure of the chest wall ($P_{el,w}$) and any net pressure due to muscle contraction (P_{mus}):

$$P_{pl} = P_{el,w} + P_{mus} \tag{10}$$

The transmission of abdominal pressure (P_{ab}) across the diaphragm influences pleural pressure. In equation (10), abdominal pressure is considered a component of $P_{el,w}$ + P_{mus}.

This model of the respiratory system forms the basis for the current understanding of respiratory mechanics, which will be discussed in the following sections.

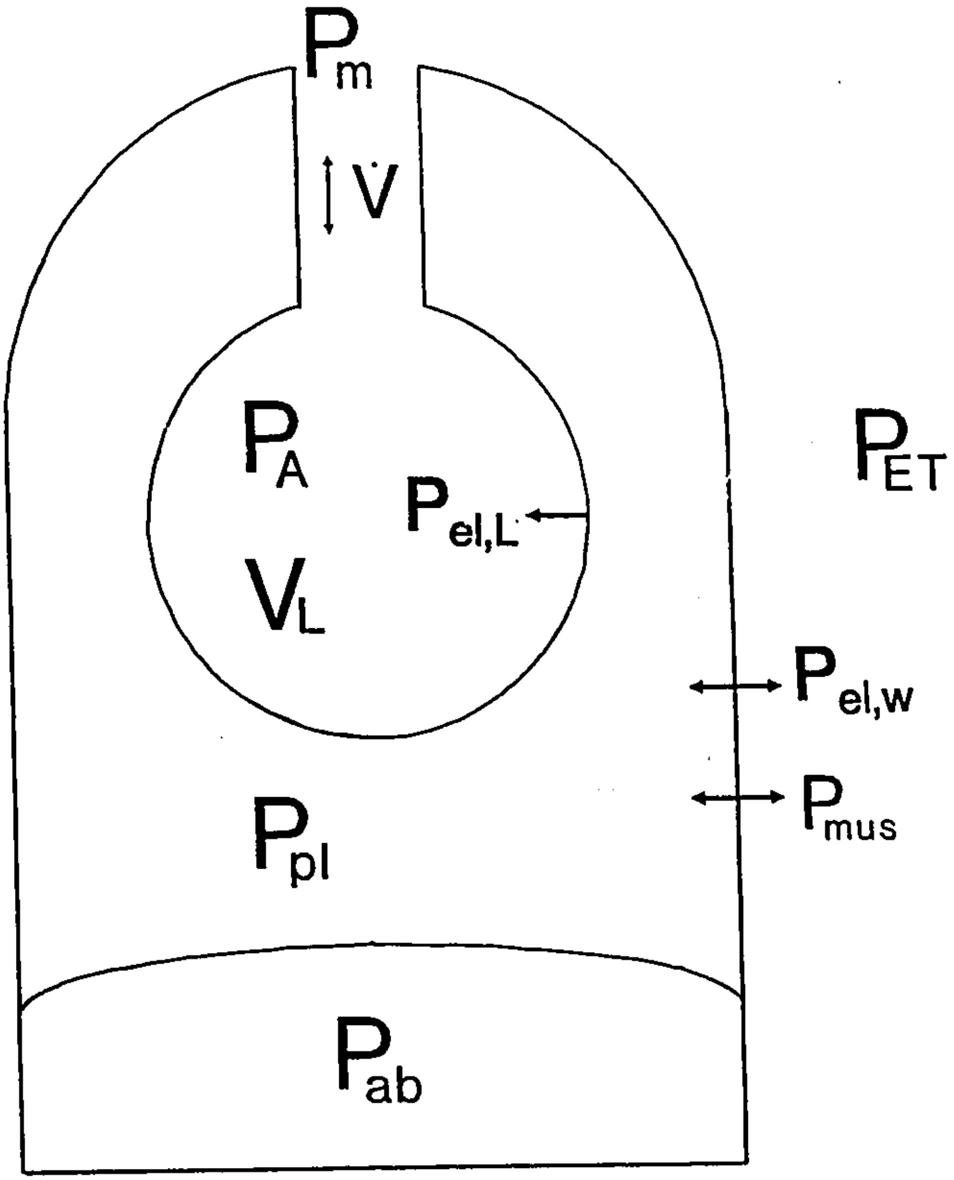


Fig 4 Simple model of the thorax, including pressures within (alveolar - P_A; pleural - P_{pl}) and adjacent (mouth -P_m; abdominal - P_{ab}; extrathoracic - P_{ET}) to the thorax, as well as potential sources of pressure (lung elastic recoil - $P_{el,L}$; chest wall elastic recoil - $P_{el,w}$; ventilatory muscle - P_{mus}). Also included as components of the model are lung volume (V_L) and rate of airflow through the airway ($\dot{V}$).

STATICS

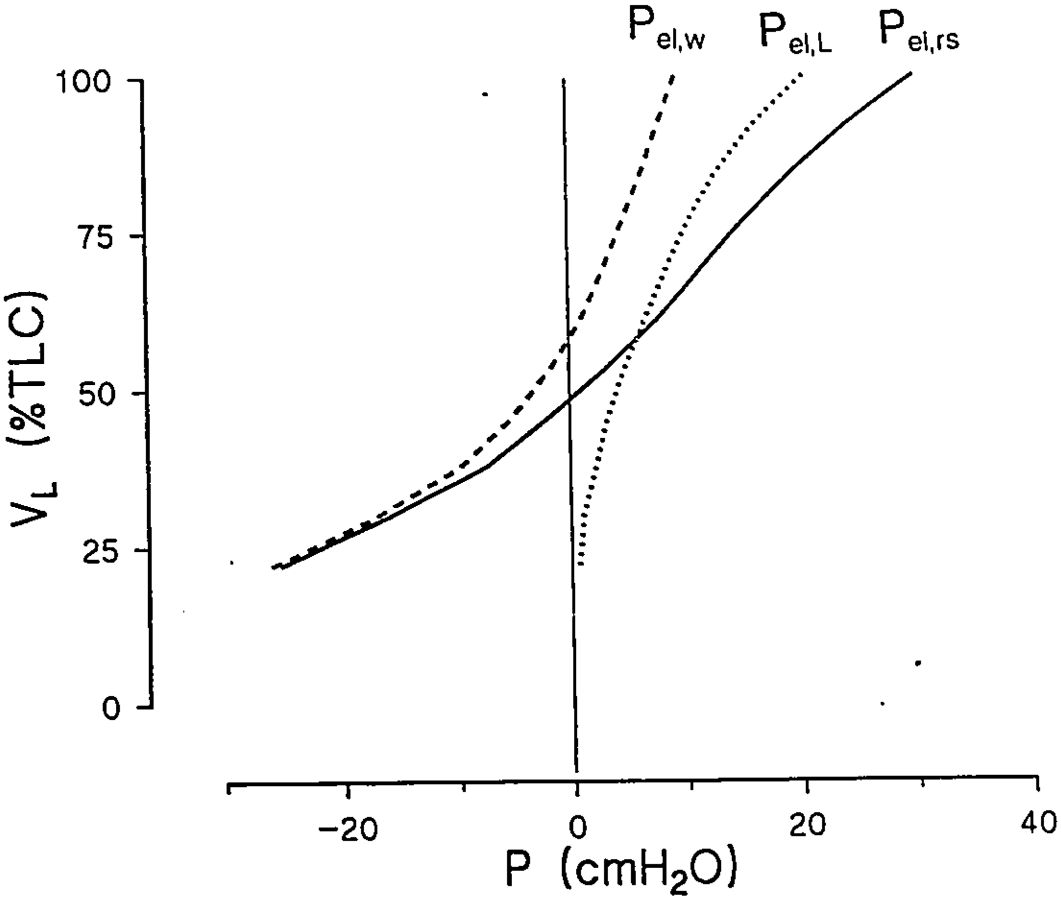
Elastic Recoil

The pressure due to the elastic recoil of the total respiratory system ($P_{el,rs}$, ie. $P_{el,L}$ plus $P_{el,w}$) was measured in a single subject by Rohrer (1916), during relaxation at several lung volumes with connection of the airway to a water manometer. This technique was also employed by Rahn et al. (1946). The recoil curve found by these authors is presented in fig 5. A similar curve to that presented was found by Heaf and Prime (1956), when they applied a constant pressure to the mouth of spontaneously breathing subjects, and measured the increase in end-expiratory lung volume. These authors assumed that the increase in EELV was proportional to the elastic recoil of the respiratory system and that no muscles were active at end-expiration.

The ability of subjects to voluntarily relax their ventilatory muscles is variable. Nims et al. (1955) found that pressure at the mouth was greater following anaesthesia and neuromuscular blockade than during voluntary relaxation, suggesting continued inspiratory activity during relaxation. Howell and Peckett (1957) also observed subjects under anaesthesia and neuro-muscular blockade and found that with practice, most subjects are able to relax their ventilatory muscles.

By monitoring esophageal pressure (Dornhorst and Leathart, 1952; Fry et al.1952), attempts were made to partition $P_{el,rs}$ measured during relaxation into the components $P_{el,L}$ and $P_{el,W}$. Ferris et al. (1952) made the first use of esophageal pressure to estimate chest wall and lung elastance (E_W and E_L) in patients with poliomyelitis and normal subjects. In the normal subjects, E_W at resting end expiratory volume averaged 4.2 cmH_2O/L, while E_L averaged 4.4 cmH_2O/L. Heaf and Prime (1956) measured E_W and E_L by monitoring esophageal pressure while applying mouth pressure resulting in end expiratory lung volume changes of 1 and 2 L above resting levels. E_W was greater at the lower volume (5.29 vs 4.48 cmH_2O/L) while E_L was less at this volume (5.23 vs 6.02 cmH_2O/L). Hence, the elastance of both structures is dependent on the lung volume.

Knowles et al. (1959) established curves describing the elastic properties of the lung and chest wall over a range of V_L. In this study, the pressure required to overcome $P_{el,L}$ was measured as the P_{es} required to maintain a given static V_L with an open glottis. The pressure required to overcome $P_{el,W}$ was measured as P_{es} while the subject relaxed against an occluded airway at a given V_L. These curves describing $P_{el,W}$ and $P_{el,L}$ are included in fig 5. $P_{el,L}$ is such that the recoil pressure is positive (tending to collapse the lungs) at any lung volume but that the slope of the curve (compliance, or elastance^{-1}) decreases as lung volume increases. $P_{el,W}$ on the other hand is such that the recoil pressure is negative (tending to inflate the lungs) at lung volumes below approximately 60% VC and becomes positive (tending to collapse lungs) above this volume. Thus, there exists a volume where the pressure generated by the lungs, favoring collapse, is exactly matched by that generated by the chest wall, favoring inflation. This would be the lung volume if no other pressures were imposed on the respiratory system, and is defined as functional residual capacity (Grassino et al.1991).



<u>Fig 5</u> An illustration of pressures generated by elastic recoil of the total respiratory system ($P_{el,rs}$), the chest wall ($P_{el,w}$) and the lung ($P_{el,L}$) as measured by Rahn et al. (1946) and Knowles et al. (1959).

Hysteresis

The curves in fig 5 indicate that the chest wall and lung develop a fixed elastic recoil pressure at a given lung volume. However, the recoil pressure developed by these structures is not stable and is subject to hysteresis, dependant on the volume history of the respiratory system (Butler, 1957; Turner et al.1967). Butler et al. (1957) measured $P_{el,W}$ and $P_{el,L}$ in anaesthetized subjects at several lung volumes while the lung was passively inflated and deflated. The recoil developed by both the lung and chest wall was greater during inflation than during deflation. Furthermore, the magnitude by which the recoil pressure during inflation exceeded that during deflation was found to vary with the extent to which the lung had been inflated. Sharp et al. (1967) found that the area contained within a hysteresis loop accounted for approximately 6% of the total elastic work done during a breathing cycle.

The Campbell Diagram

Up to this point, $P_{el,L}$ and $P_{el,W}$ have been expressed in terms of the pressure measured at the mouth as a result of recoil of the lung and chest wall. Thus, in fig 5 above 60% TLC, both $P_{el,L}$ and $P_{el,W}$ develop positive recoil pressures, while below 60% TLC, $P_{el,W}$ develops negative pressure. While this is a logical approach to take when one is interested in the pressures imposed by the lung and chest wall on the respiratory system, Campbell (1958) has suggested another approach, which is more appropriate when one is interested in the pressures that must be imposed on the respiratory system in order to displace these structures. This approach is illustrated in fig 6, where the $P_{el,L}$ curve from fig 5 has been replaced by748XtBe$_{pl\text{-}stat}$ curve, reflecting the pleural pressure required to oppose lung elastic recoil at any given V_L under static conditions.

Unless a pressure is imposed on the respiratory system, P_{pl} will be approximately -5 cmH_2O, opposing $P_{el,L}$ and $P_{el,w}$ and holding V_L at FRC (fig 6). For V_L to be at any other static volume than FRC, E_w and E_L are no longer in balance and muscular pressure (P_{mus}) must be generated. The balance between muscle and elastic pressure sources is given by the following equation:

$$P_{mus} = P_{el,w} - P_{pl\text{-}stat} \; (+ P_A) \tag{11}$$

The P_A term is in brackets, as it would always be zero under static conditions with the glottis open. Whenever P_{pl} falls to the left of the $P_{el,w}$ curve, inspiratory muscles must be active, while P_{pl} to the right of the $P_{el,w}$ curve indicates expiratory muscle activity. Hence, to raise V_L above FRC requires inspiratory muscle activity, while lowering V_L below FRC requires expiratory activity.

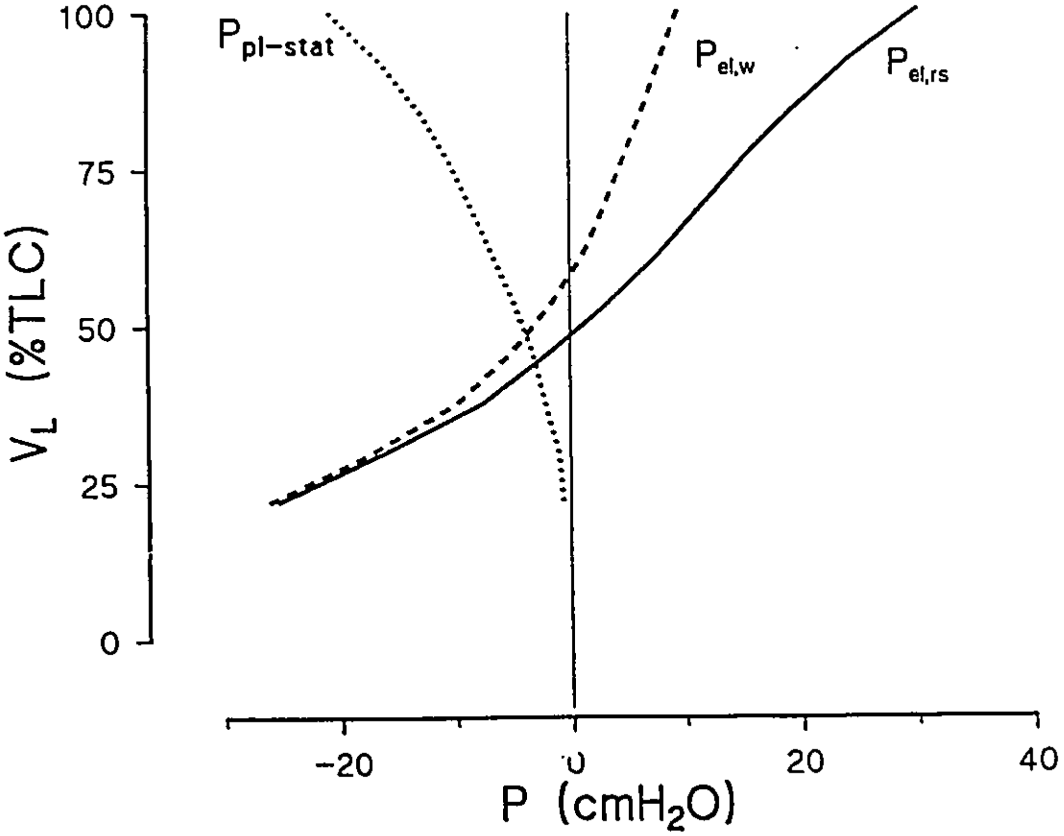


Fig 6 The Campbell diagram. A redrawing of fig 5, with the $P_{el,L}$ curve replaced by the $P_{pl\text{-}stat}$ curve, depicting the pleural pressure required to oppose the elastic recoil of the lung.

Muscle Pressures

Rohrer (1916) and Rahn et al. (1946) measured the pressure that could be developed at the mouth through maximum inspiratory and expiratory effort at several static lung volumes. The findings of these investigations for inspiration (MIP_{stat}) and expiration (MEP_{stat}) are summarized in fig 7. The pressure developed by the inspiratory muscles is maximal at lung volumes below FRC and decreases as V_L increases. Pressure developed by the expiratory muscles is maximal at TLC and decreases as V_L decreases. This finding is consistent with the known length tension relationships of skeletal muscle (Evans and Hill, 1914), but may also reflect the complex geometry of respiratory muscle contraction, particularly the curvilinearity of the diaphragm.

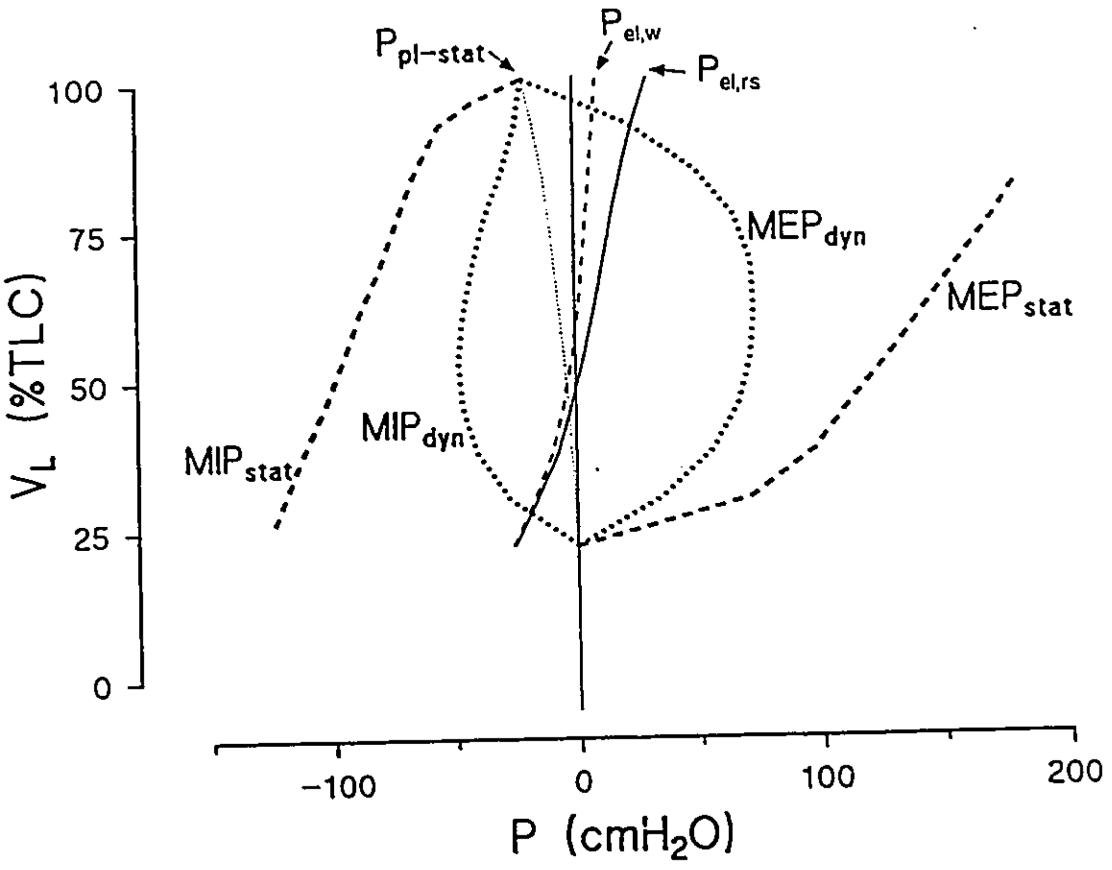


Fig 7 Maximal static and dynamic muscle pressures illustrated on the Campbell diagram. Based on measures by Rahn et al. (Rahn et al.1946) and Agostoni and Fenn (Agostoni and Fenn, 1960) during maximal inspiratory (MIP) and expiratory (MEP) efforts at a variety of lung volumes under static ($_{stat}$) and dynamic ($_{dyn}$) conditions.

DYNAMICS

In fig 6, the $P_{pl\text{-}stat}$ and $P_{el,w}$ curves represent the pressures that must be generated to overcome the elastic components of the respiratory system. During ventilation, pressure must also be generated to overcome resistance and inertia.

The three different components of the respiratory system that may offer resistance to flow are airway (R_{airway}), lung tissue (R_L) and chest wall tissue (R_w) (Rodarte and Rehder, 1986). These components of resistance will be described with reference to the model of the respiratory system presented in fig 4.

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Airway resistance is responsible for the gradient between the alveolar and mouth pressure (P_m) during constant flow expiration or inspiration ($\dot{V}_L$):

$$R_{airway} = \frac{P_m - P_A}{\dot{V}_L} \tag{12}$$

Lung tissue resistance is responsible for the pressure gradient between the alveoli and pleural space other than that owing to lung recoil, during constant flow procedures:

$$R_L = \frac{(P_{pl} - P_A) - P_{el,L}(V_L)}{\dot{V}_L} \tag{13}$$

where $P_{el,L}(V_L)$ is the recoil pressure of the lung at the lung volume at which R_L is being measured.

Because determination of both R_{airway} and R_L depend on an approximation of P_A, these two resistances are often considered together as pulmonary resistance (R_{pulm}). As R_{airway} and R_L are in series, R_{pulm} is equal to their sum, and given by the following equation:

$$R_{pulm} = \frac{(P_{pl} - P_m) - P_{el,L}(V_L)}{\dot{V}_L} \tag{14}$$

The final component of respiratory system resistance is that related to the chest wall. This is the resistance associated with a pressure gradient across the chest wall other than that owing to chest wall recoil, during conditions of constant flow. R_w is thus given by the following equation:

$$R_w = \frac{(P_{ET} - P_{pl}) - P_{mus} - P_{el,w}(V_L)}{\dot{V}_L} \tag{15}$$

where $P_{el,w}(V_L)$ is the recoil pressure of the chest wall at the lung volume at which R_w is being determined.

Pulmonary Resistance

R_{pulm} can be determined by measuring flow rate and esophageal pressure simultaneously. Provided that the static properties of the lung are also known, all the variables of equation (13) are then available. Fry et al. (1954) analyzed R_{pulm} based on this principle and found that R_{pulm} decreased linearly as V_L increased. Briscoe and DuBois (1958) using a technique for determining P_A under dynamic settings (DuBois et al.1956), found that the decline in R_{pulm} with increasing V_L was a result of a decrease in R_{airway}, presumably owing to an increase in airway diameter.

Maximum Effective Pressure

The observation that R_{pulm} is influenced by V_L is true for both inspiration and expiration (Fry et al.1954), however, during expiration R_{pulm} is also influenced by P_{pl}. Observing fig 4, one can see that large positive P_{pl} is transmitted across the alveolar membrane creating a large $P_A - P_m$ gradient, favoring expiratory flow. However, much of the airway is also exposed to P_{pl}, which would tend to compress it and increase R_{pulm}. As P_{pl} is increased above a certain level, the increase in R_{pulm} is such that no further increases in expiratory flow are observed (Fry et al.1954). Pride et al. (1967) actually measured a levelling off followed by decreases in airflow as P_{pl} was increased. The maximum P_{pl} that is associated with increasing expiratory flow will be referred to as the maximum effective pressure (P_{maxeff}). The relationship between P_{maxeff} and V_L as measured by Hyatt and Flath (1966) in normal subjects is illustrated in fig 8. The shaded area in fig 8, where pressure is greater than $P_{el,w}$ but less than P_{maxeff} indicates where expiratory activity is used to increase expiratory flow. During inspiration P_{pl} is always negative, tending to increase airway diameter and therefore, there is no inspiratory P_{maxeff}.

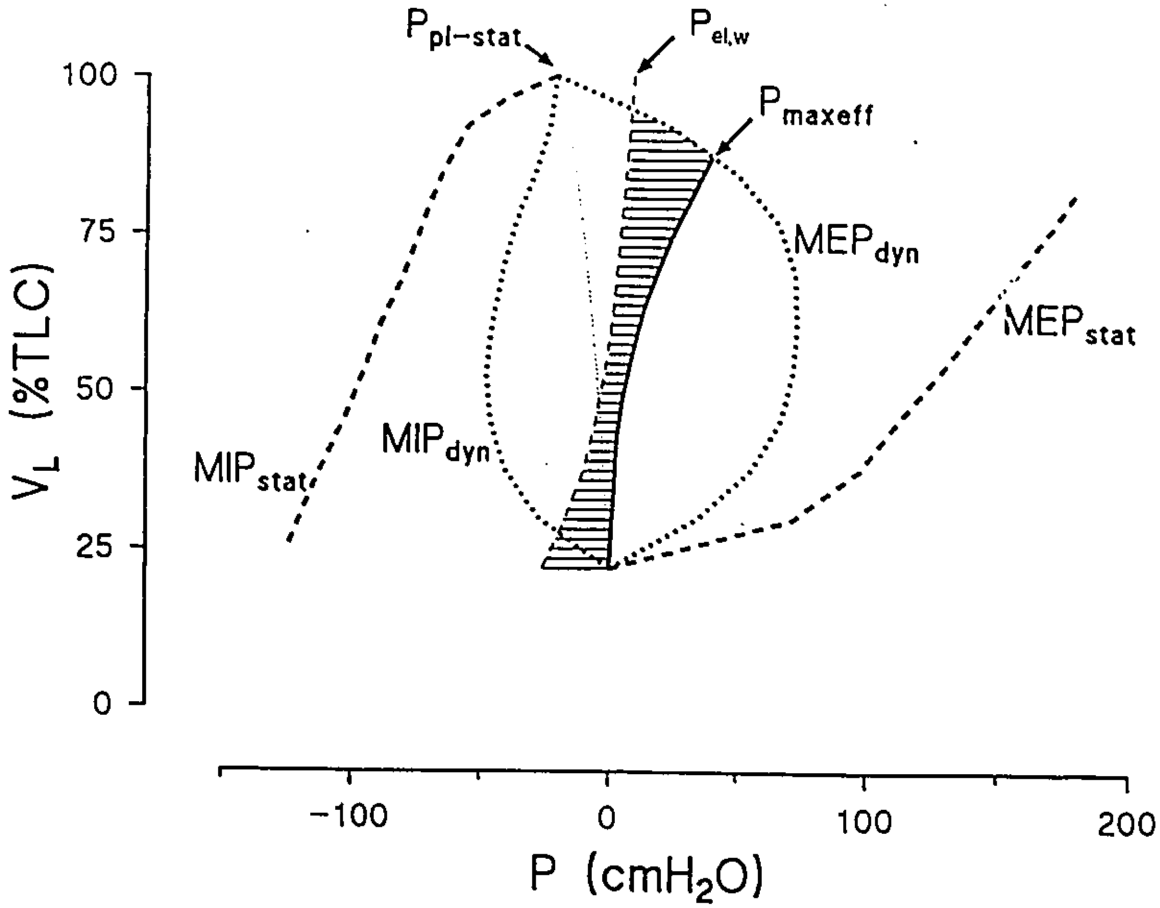


Fig 8 Maximum effective pressure illustrated on the Campbell diagram. P_{maxeff} curve is based on measures by Hyatt and Flath (Hyatt and Flath, 1966) under resting conditions. Shaded area represents region where pressures may be generated by expiratory muscle that would result in increased expiratory flow.

Chest Wall Resistance

Because an approximation of R_w is used in this thesis to calculate work of breathing, review of the techniques used for its determination will be performed in detail. P_{mus} must be accounted for in the calculation of R_w (see equation (14)). As there is no means of measuring P_{mus}, investigators have been forced to determine R_w in settings where P_{mus} is assumed to be zero (Opie et al.1959; McIlroy et al.1963) or by applying pressure gradients across the chest wall while assuming constant P_{mus} (Ferris et al.1964; Sharp et al.1964; Fisher et al.1968; Grimby et al.1968; Goldman et al.1970; Barnas et al.1987; Hantos et al.1986; Albright and Bondurant, 1965; Barnas et al.1989; Barnas et al.1989)

The first attempt to measure R_w was made by Opie et al. (1959) when they ventilated paralysed subjects with intermittent positive pressure at the mouth while monitoring esophageal pressure. $P_{el,w}$ was determined under static conditions. Knowing $P_{el,w}$ allowed the elastic component of the esophageal pressure signal to be subtracted from that recorded during dynamic measures. R_w was calculated based on this corrected pressure signal and airflow measured in the ventilator tubing. R_w averaged 0.5 $cmH_2O/L/s$ when measured in three subjects during inspiration at approximately 0.5 l/s. McIlroy et al. (1963) had subjects perform relaxed expirations, while monitoring P_{es}, lung volume change and expiratory flow. Under these conditions, measures of R_w

averaged 2.75 cmH_2O. indicating wide variability in the measurement.

Much of the current understanding of R_w in normal subjects is based on the forced oscillation technique developed by DuBois et al. (1956) for determining total thoracic resistance. This technique is based on generating a sinusoidal airflow at the airway. If the respiratory system offered purely resistive impedance, then the resulting pressure changes would also be sinusoidal and in phase with the flow signal. However, the actual pressure changes are also influenced by the elastic and inertial properties of the respiratory system. The elastic component of the pressure response is in phase with volume changes, and thus lags behind the flow signal by ¼ cycle (90° phase shift). The inertial component of the pressure response is in phase with acceleration and thus precedes the flow response by ¼ cycle (-90° phase shift). Thus, the components of the pressure signal proportional to volume and acceleration changes are 180° out of phase. Because the fraction of the driving pressure required to overcome elastance is inversely proportional to frequency, while that required to overcome inertia is directly proportional to frequency, it is theoretically possible to apply forced oscillations at a frequency (resonant frequency) where the elastic and inertial components of the pressure response effectively cancel each other out. While oscillating at this frequency (approximately 5 Hz), resistance can be determined by simply observing the relationship between applied pressure and resulting flow. Based on this principle, DuBois et al. (1956) measured the resistance of the respiratory system (R_{rs}) to be 4.6 $cmH_2O/L/s$. Mead et al. (1960) adapted the forced oscillation technique so that it could be applied to subjects breathing spontaneously in a body box. By generating resonant frequency sinusoidal pressure fluctuations in the body box, these authors measured R_{rs} to be 5.5 $cmH_2O/L/s$. Ferris et al. (1964) using the adapted technique of Mead et al. (1960) in conjunction with measures of esophageal pressure were able to partition R_{rs} into the components R_{pulm} and R_w. These authors found that R_w was 0.5 $cmH_2O/L/s$.

Using the same technique, Sharp et al. (1964) also measured R_w of 0.5 cmH_2O. However. these investigators also measured R_w by ventilating relaxed subjects at low frequencies (0.2, 0.33, 0.5 Hz) and found a significantly greater value of 3.4 $cmH_2O/L/s$. Hence, the value of R_w might be sensitive to ventilatory frequency. This was confirmed by Albright and Bondurant (1965), Grimby et al. (1968), Hantos et al, (1986) and Goldman et al. (1970) when they found that lower frequency oscillations resulted in higher measures of R_w.

Hantos et al. (1986) suggested that the frequency dependence of R_w might be due to non-uniformity of chest wall movement at different frequencies, with regional differences in tissue properties. However, Barnas et al. (1987) used magnetometers and observed uniform chest wall movement over a range of frequencies (0.2 to 4 Hz) associated with large changes in R_w. Tidal volume was held constant at approximately 1/5 of the subject's vital capacity. These findings indicated that the frequency dependence of R_w was not due to non-uniform chest movement but rather to viscoelastic properties of the chest wall. The relationship between R_w and frequency in that study is given in the following equation:

$$R_{cw} - 0.49 + \frac{0.43}{f} \quad (cmH_2O/L/s) \qquad (r^2 - 0.98) \qquad \textbf{(16)}$$

where f is in Hz. The authors suggested that the observation of a frequency dependence of R_w is due to viscoelastic properties of the chest wall, such that pressure is required for distortion of plastic like components of chest tissue.

The magnitude of viscoelastic dissipation of pressure is dependent on volume change. The magnitude of pressure required to overcome true R_w (ie. not including the viscoelastic component) is dependent on flow. Thus, the viscoelastic component will play a relatively decreasing role in apparent R_w as flow increases. Hence, Barnas et al (1987) suggest that the frequency dependent component of equation (16) ($0.43/f$ cmH$_2$O/L/s) is that owing to plastic dissipation of pressure, while the constant component (0.49 cmH$_2$O/L/s) is the true R_w. Obviously, to calculate the pressure required for the velocity component of chest wall motion the apparent

R_w (given by equation (16)) would have to be accounted for, not merely the true R_w.

In a later study, Barnas et al. (1987) varying both f and V_T found that apparent R_w was influenced by tidal volume as well as frequency. In that study, R_w was calculated using the forced oscillation technique described above, while varying tidal volume (250, 500 and 750 mL) at each of three frequencies (0.2, 0.4 and 0.6 Hz). While the authors report a significant effect of both variables on apparent R_w, they did not give the regression equation required for determining apparent R_w. A regression performed on the mean data (presented in their figure 3) resulted in the following equation:

$$R_{cw} = -1.365(\ln(f) -0.506(\ln(V_T) -0.437 \quad (cmH_2O/L/s) \tag{17}$$

where, f is in Hz and V_T in L. This equation accounts for 94% of the variation in the mean data of Barnas et al (1989). Unfortunately, the ranges of f and V_T employed in that study do not cover those observed during exercise. However, it appears from their results (figure 3 from (Barnas et al.1989)) that as either f or V_T is increased beyond the range of the study, pressures dissipated in tissue viscoelastance will be minimal and apparent R_w will be equal to the true R_w of 0.49 $cmH_2O/L/s$ (Barnas et al.1987). Equation (17) was used to predict R_w in this thesis, except in cases where the prediction was less than 0.49 $cmH_2O/L/s$, where a value of 0.49 $cmH_2O/L/s$ was used.

The measures of apparent R_w made by Barnas et al. (1987; 1989) were performed while the subjects were relaxed at FRC. Whether the relationship between measured R_w and f and V_T in equation (17) holds true for a spontaneously breathing subject depends on whether apparent R_w measured with relaxed muscles reflects that with active muscles. Barnas et al. (1989) have attempted to resolve this by having subjects perform sustained inspiratory or expiratory efforts while measuring R_w. In that study, R_w was measured using the forced oscillation technique over a range of f with V_T held constant (5-8 %VC) while subjects performed sustained inspiratory or expiratory efforts of -10, -5, 5 and 10 cmH_2O. These authors found that both inspiratory and expiratory efforts resulted in higher measures of R_w. Measures at 0.5 Hz were approximately 2 $cmH_2O/L/s$ when subjects were relaxed, approximately 5 $cmH_2O/L/s$ with 5 cmH_2O inspiratory or expiratory effort and 10-15 $cmH_2O/L/s$ with 10 cmH_2O inspiratory or expiratory effort. A problem with these findings is that the inspiratory or expiratory effort by the subject was sustained throughout the breathing cycle. Thus, under conditions of inspiratory effort, the subject was actively inspiring during the expiratory as well as the inspiratory phases of the forced oscillation. One would expect that inspiratory effort would offer greater resistance to expiration than inspiration. Unfortunately the authors do not say whether R_w was measured during the inspiratory, expiratory or both phases of the oscillation. In early studies by the same group using this technique (Mead, 1960), resistance was calculated as the ratio of the total amplitude of the velocity component of the pressure signal to the total amplitude of the flow signal, and thus reflects the average of inspiratory and expiratory resistances. It appears that muscle activity may influence apparent R_w, but more information is needed to determine to what extent this occurs when the direction of activity (inspiratory or expiratory) is the same as the direction of flow.

Frequency and Volume Dependence of $P_{el,w}$

Earlier in this chapter, a single curve based on static measures by Knowles et al. (1959) was used to represent the recoil pressure of the chest wall (see $P_{el,w}$ on figs 5 and 6). Based on this curve, the elastance of the chest wall (E_w) in the region above FRC is approximately 5 cmH$_2$O/L. However, results obtained using forced oscillation techniques indicate that E_{rs} may be dependent on both frequency and tidal volume.

Barnas et al. (1987) measured increases in E_{rs} from approximately 10 cmH$_2$O/L at f of 0.2 Hz, to 15 cmH$_2$O/L at f of 2 Hz. However, further studies by this group have not shown frequency dependence of E_{rs} during forced oscillations at frequencies expected during spontaneous breathing (f varied between 0.2 and 0.6 Hz) (Barnas et al.1989).

While it does not appear that *f* affects $P_{el,w}$ during spontaneous breathing Barnas et al. (1989) have shown that forced oscillation measures of E_w vary with tidal volume. Measures of E_w fell in a linear manner from approximately 11 cmH_2O/L to approximately 7 cmH_2O/L as forced tidal volume was increased from 0.25 L to 0.75 L (Barnas et al.1989). Whether E_w would continue to decrease with greater tidal volumes has not been studied. Unfortunately these findings can not be used to correct the $P_{el,w}$ curve for different tidal volumes. While the E_w could be predicted for a given tidal volume, the absolute recoil pressure at specific lung volumes would not be known. Hence, the $P_{el,w}$ curve in fig 5, determined under static conditions reflects the recoil pressure of the chest wall, but the precision is questionable.

Muscle Pressures

The curves illustrating the pressures that can be generated through maximal effort under static conditions have already been presented (fig 7). Based on observations made by Fenn and Marsh (1935), it is known that the tension developed by a maximally activated skeletal muscle decreases as the velocity of contraction increases. This relationship also exists for respiratory muscles. Agostoni and Fenn (1960) measured mouth pressure during maximal inspirations and expirations against several levels of resistance to airflow.

With maximal resistance (ie, zero flow) the pressure developed was similar to the MIP_{stat} and MEP_{stat} curves presented in fig 7. As resistance was decreased, airflow increased and there was a resultant decrease in the pressure developed at any given V_L, as expected based on the earlier work of Fenn and Marsh (1935). The pressures developed with minimal external resistance are presented for inspiration (MIP_{dyn}) and expiration (MEP_{dyn}) in fig 7, these represent the maximal pressures developed by the respiratory muscles under nearly unimpeded conditions.

Inertia

Respiratory muscle pressure must overcome the inertia offered by the respiratory system (air and tissues). The pressure required to overcome inertia can be partitioned using equations similar to those describing the resistive and elastic components of pressure. However, there is evidence that inertial impedance is small and this component of pressure is negligible. DuBois et al. (1956) estimated the inertia of the respiratory system by measuring its natural frequency (f_n), estimating the elastance of the respiratory system (E_{rs}) and using the following equation describing second order systems (physical systems containing elastance, resistance and inertia):

These authors calculated a value of 0.0057 $cmH_2O/L/s^2$. Sharp

$$f_n = \frac{1}{2\pi} \cdot \left(\frac{E_{rs}}{I_{rs}}\right)^{\frac{1}{2}} \qquad (18)$$

et al. (1964) performed a similar analysis on subjects whose E_{rs} had been measured and found a mean value for I_{rs} of 0.0098 $cmH_2O/L/s$. Hence, even at maximal exercise, where volume acceleration may reach levels of 100 L/s/s, the peak pressure needed to overcome inertia is less than 1 cmH_2O.

WORK OF BREATHING

Theoretical Estimates, Based on Equation of Motion

The work performed by the respiratory system can be calculated as the product of the driving pressure and the resulting change in volume. Otis et al. (1950) using the assumption that V_L fluctuated as a sine function during normal breathing, developed the following equation to calculate the work performed during an inspiration (W_{insp}):

$$W_{insp} = \frac{E}{2} \cdot V_T^2 + \frac{K_1}{4} \cdot \pi^2 f V_T^2 + \frac{2K_2}{3} \cdot \pi^2 f^2 V_T^3 \qquad (19)$$

where, E is elastance, V_T is tidal volume, f is frequency and K_1 and K_2 are constants related to resistance. The first term reflects work done overcoming elastance, the second reflects work done overcoming resistance proportional to flow and the third reflects work done overcoming resistance proportional to the square of flow; inertia was assumed negligible. Otis et al. (1950) argued that work done during expiration will be accounted for in the first term if expiration is passive and thus, equation (19) reflects the work done throughout a complete ventilatory cycle. If however, expiration is active, then work done throughout a complete cycle may be approximated by doubling the second two terms. Otis et al. (1950) differentiated the resulting equation to obtain an equation for power, equal to the mechanical work of ventilation per unit time ($\dot{W}$):

$$\dot{W} = 2\left(\frac{K_1}{4}\cdot\pi^2 \dot{V}_E^2 + \frac{2K_2}{3}\cdot\pi^2 \dot{V}_E^3 \right) \qquad (20)$$

Analyses of the work of breathing based on the equation of motion rely on several assumptions, the most obvious of which is that the volume signal during ventilation follows a sine wave pattern. While it is possible to alter K_1 and K_2 to account for any breathing pattern, as has been done by Lafortuna et al. (1984) for patterns observed during exercise, this approach does not result in a general equation.

A second assumption is that the respiratory system offers constant resistance to flow. This does not take into account the already mentioned viscoelastic properties displayed by tissue. Milic-Emili (1991) has modified equation (20) so that it takes into account the frequency dependence of apparent resistance (viscoelastance). Furthermore, the approach assumes that the work done to achieve a given change in volume at a given flow rate during expiration is the same as that for inspiration. It has already been mentioned that pulmonary resistance increases during active expiration, when the increased pleural pressure results in airway compression (Hyatt and Flath, 1966). In assuming that pulmonary resistance is the same during expiration as inspiration, there is the potential to underestimate the mechanical work performed by the expiratory muscles.

Integration of Pressure-Volume Loops

Rohrer (1925) described an approach for determining the work of breathing based on the integration of pleural pressure with respect to volume. McIlroy et al. (1954), using esophageal pressure as an index of pleural pressure adapted the technique for measuring work in spontaneously breathing human subjects, while Margaria et al. (1960) made further adaptations so that the technique became based on the Campbell diagram described earlier.

Fig 9 is an illustration of the P_{pl} occurring during an inspiration and expiration. One can see that at the onset and completion of inspiration, P_{pl} lies on the $P_{pl\text{-}stat}$ curve. During the course of inspiration, P_{pl} is more negative than $P_{pl\text{-}stat}$ at the same volume. The pressure difference between P_{pl} and $P_{pl\text{-}stat}$ is that required to overcome R_{pulm}. The same occurs during expiration, except that P_{pl} is more positive than $P_{pl\text{-}stat}$, with the difference again representing the pressure required to overcome R_{pulm}. Also included in this figure is an illustration of the pressure required to overcome R_w. This pressure is illustrated as the difference between the E_w curve and the dashed loop. Calculation of the work of breathing from fig 9 requires accounting for pressures that overcome elastance and resistance and determining whether the source of those pressures is from elastic recoil or muscle. This may be done using the following guidelines:

Partitioning of work of breathing:

Resistive:

1/ All area between P_{pl} curve and $P_{pl\text{-}stat}$ curve is work done overcoming R_{pulm}.

2/ All area between $P_{el,w}$ curve and dashed line is work done overcoming R_w.

Elastic:

1/ All area between either recoil curve ($P_{pl\text{-}stat}$, $P_{el,L}$) and the zero pressure line during the movement of that structure in a direction opposite to its recoil tendency is work done overcoming elastance.

Pressure source for work of breathing:

Elastic recoil:

All area between either recoil curve (chest wall and lung) and the zero pressure line during the movement of that structure in a direction equal to its recoil tendency is work performed by elastic recoil of that structure.

Muscle:

All area unaccounted for by elastic recoil is work performed by muscle. If this area is to the left of the $P_{el,w}$ curve then the work is performed by inspiratory muscles, if it is to the right, work is performed by expiratory muscles.

Fig 10 is similar to that presented by Agostoni et al. (1970), based upon the guidelines (above), and illustrates the various components of work done during inspiration and expiration.

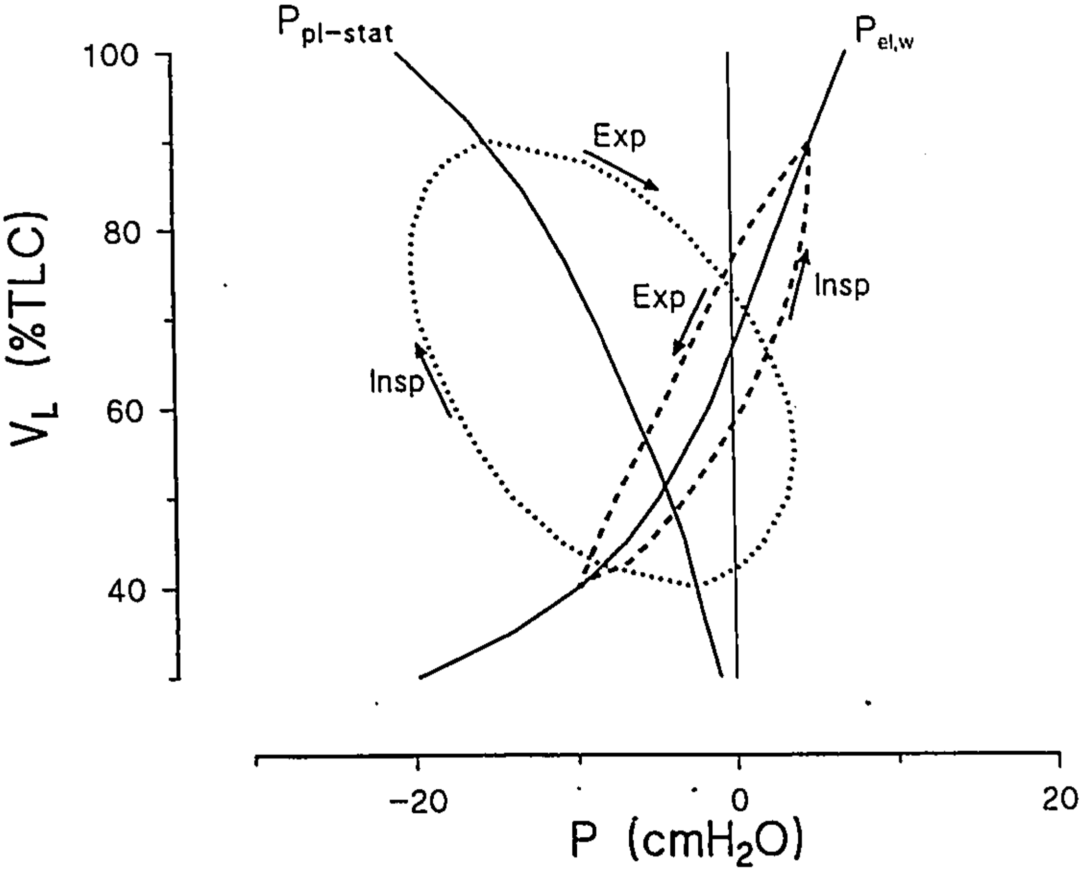
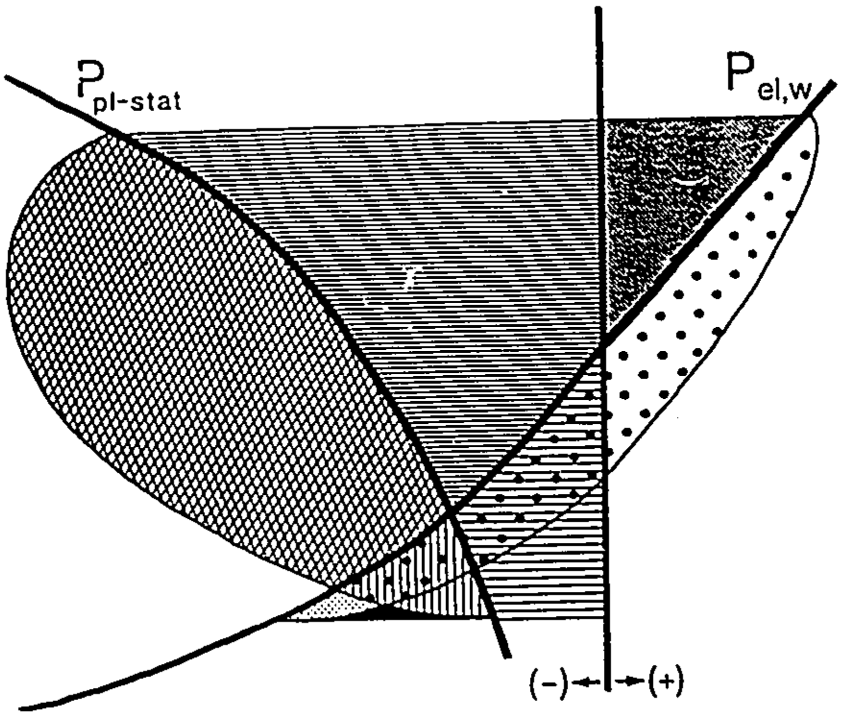
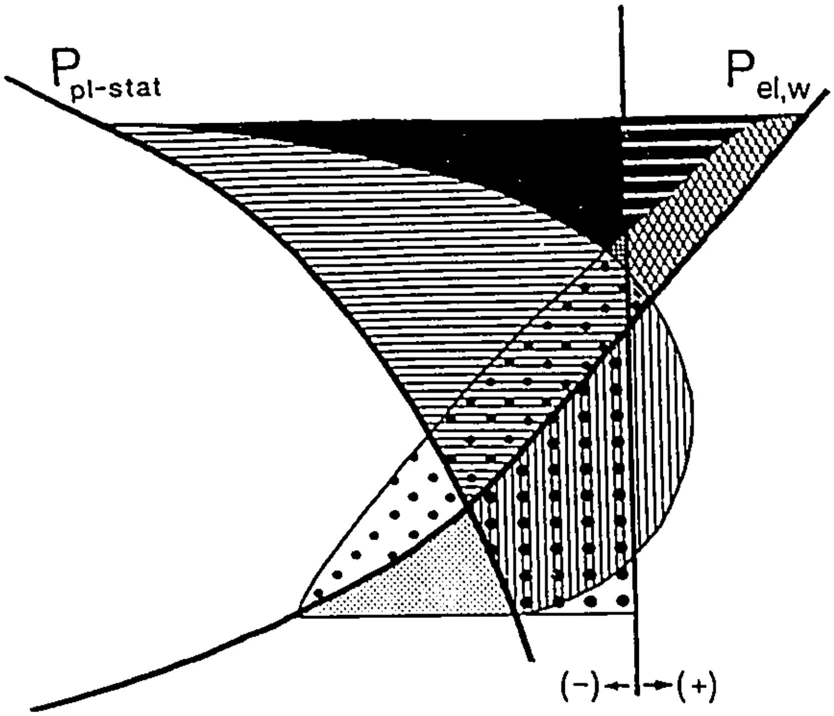


Fig 9 Campbell diagram illustrating the pressure required to overcome pulmonary and chest wall resistance. The dotted loop represents pleural pressures throughout a breath; the pressure difference between this and $P_{pl-stat}$ represents that required to overcome R_{pulm}. The difference between the dashed loop and $P_{el,w}$ represents the pressure required to overcome R_w.



		Work Done By:	Work Done On:
▓	A	Inspiratory Muscle	Chest Wall Recoil
▤	B	Inspiratory Muscle	Lung Recoil
▦	C	Inspiratory Muscle	Pulmonary Resistance
⁘	D	Inspiratory Muscle	Chest Wall Resistance
▤	E	Chest Wall Recoil	Lung Recoil
▥	F	Chest Wall Recoil	Pulmonary Resistance
░	G	Chest Wall Recoil	Chest Wall Resistance
■	H	Expiratory Muscle (-)	Chest Wall Recoil

Fig 10 Campbell diagram, illustrating the various components of work done throughout a breath. Division of work into component parts is according to guidelines described in text. Figure is based on that of Agostoni et al. (Agostoni et al.1970). This page shows inspiratory segment only, expiration found on next page.



		Work Done By:	Work Done On:
░	I	Expiratory Muscle	Chest Wall Recoil
▥	J	Expiratory Muscle	Pulmonary Resistance
⁘	K	Expiratory Muscle	Chest Wall Resistance
●	L	Lung Recoil	Chest Wall Recoil
▓	M	Chest Wall Recoil	Pulmonary Resistance
▦	N	Lung Recoil	Chest Wall Resistance
▤	O	Lung Recoil	Pulmonary Resistance
▩	P	Chest Wall Recoil	Chest Wall Resistance
☰	Q	Inspiratory Muscle (-)	Chest Wall Recoil
■	R	Inspiratory Muscle (-)	Lung Recoil

Fig 10 (cont'd)

The first attempt to measure work of spontaneous breathing using this approach was that of McIlroy et al. (1954). Work was calculated with subjects breathing at rest and during light exercise. In that study however, end-expiratory pleural pressure was subtracted from pleural pressure during an inspiration and integrated with respect to volume to calculate inspiratory work. This approach does not take into account the shape of the chest wall recoil curve and thus would underestimate inspiratory work. Calculations of work in this study would also likely be low, as no attempts were made to measure work during expiration (positive expiratory work or negative work by inspiratory muscles), nor was there any mention of the work done on chest wall resistance.

Margaria et al. (1960) measured the work of breathing during exercise with ventilation up to approximately 120 L/min. Although these authors did not account for the work performed to overcome chest wall resistance, their approach was essentially as outlined in the guidelines in this section. The curve relating measured work to $\dot{V}_E$ is shown in fig 11.

Using the same technique as Margaria et al. (1960), Milic Emili et al. (1962) measured work of breathing in exercising athletes ($\dot{V}_E$ up to 180 L/min). Again, work performed on chest wall resistance was not accounted for, based on the assumption that it would only be a small fraction of the total. The results of that study are included in fig 11.

While Margaria et al. (1960) mentioned that it was possible to partition the total work into that performed by the inspiratory and expiratory muscles, this was not actually done. Thoden et al. (1969) attempted to perform this partition, using a similar approach to that of Margaria et al. (1960) (although no mention was made of the technique used to determine $P_{el,w}$ or absolute V_L). The curve relating work to $\dot{V}_E$ from this study is included in fig 11. At the maximum level of exercise ($\dot{V}_E$ = 90 L/min), muscular work of expiration accounted for approximately 4% of the total work performed. In this study, there was no mention made of the work done on chest wall resistance.

Relationships between the level of ventilation and work of breathing are shown in fig 11 (Margaria et al.1960; Milic-Emili et al.1962; Thoden et al.1969). In all studies chest wall resistance and viscoelastance were ignored under the assumption that their contribution would be small. A second possible failing of these studies is the validity of lung volume measures. Volume fluctuations were monitored using spirometer or pneumotachometer but no mention was made of how absolute lung volume was determined during exercise. Errors in the placement of the pressure-volume loop would obviously affect the calculated work.

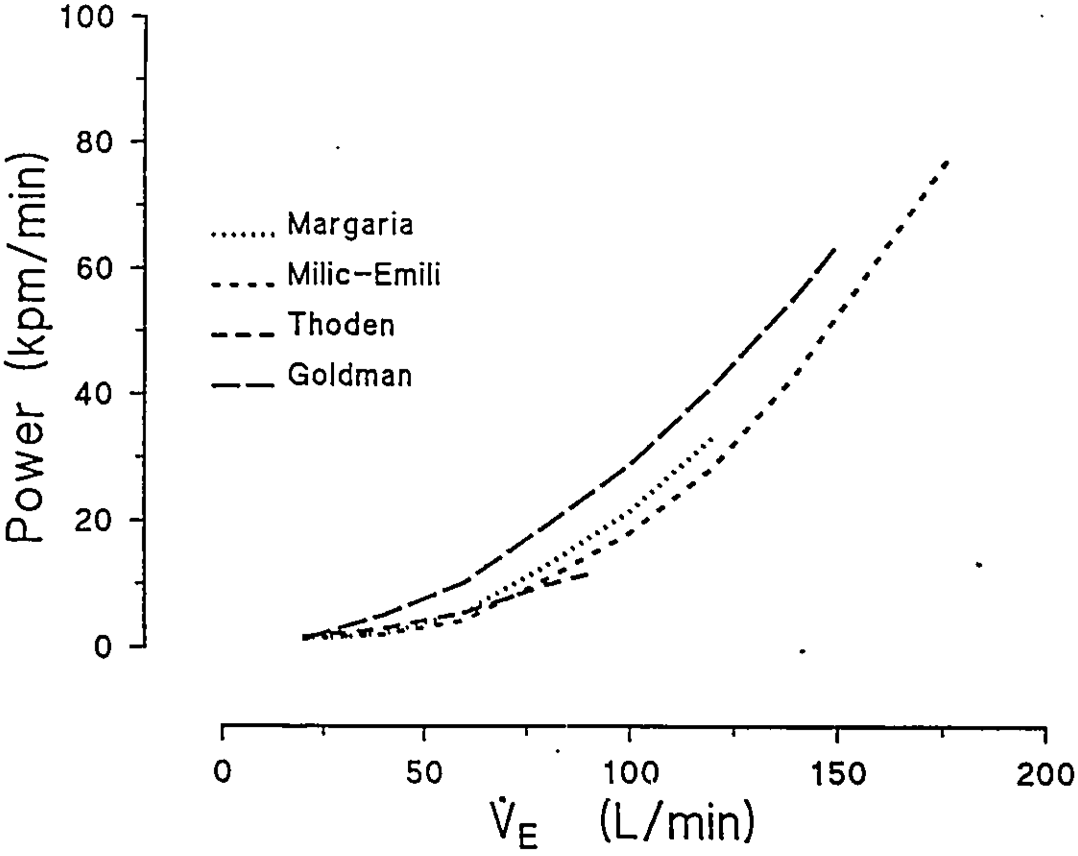


Fig 11 Power (Work/time) of breathing, measured over a range of ventilation. Based on measures of Margaria et al. (1960), Milic-Emili et al. (1962), Thoden et al. (1969) and Goldman et al. (1976).

Work Performed Owing to Chest Wall Distortion

Use of the Campbell diagram to measure the work of breathing is based on the assumption that at any given lung volume, the elastic recoil of the chest wall during breathing is the same as that measured under relaxed static conditions at the same lung volume. If this is not the case, then measured work may underestimate actual work.

Konno and Mead attempted to partition the volume displacement of the chest wall between the rib cage and the abdomen (Konno and Mead, 1967). Potentiometers were used to measure the anterior-posterior (A-P) diameter changes of the abdomen and rib cage as an index of volume changes of these compartments. Konno and Mead (1967) showed that under relaxed conditions, the chest wall behaves with a single degree of freedom. That is, with relaxation, a given lung volume was associated with a specific set of abdominal and rib cage A-P diameters. However, with muscular effort, subjects were capable of achieving a given lung volume using a range of abdominal and rib cage A-P diameters. This observation indicates the potential for chest wall distortion, resulting in two degrees of freedom in its motion. The authors pointed out that the work performed to distort the chest wall (ie. achieve a set of abdominal and rib cage A-P diameters other than those measured under relaxed conditions) would not be included using the Campbell diagram technique for measuring work of breathing.

Grimby et al. (1968) measured rib cage and abdominal A-P diameters during relaxation and during upright cycling exercise. Distortion of the chest wall did not occur during resting breathing, but did occur during exercise, such that abdominal A-P diameter was less at any given lung volume than it had been during relaxation at rest. The authors went on to suggest that the work required to achieve this distortion could be calculated, if the static characteristics of the rib cage and abdominal compartments were known, and provided the characteristics of one compartment were not influenced by a change in volume of the other compartment.

The static characteristics of the abdominal and rib cage compartments were first measured by Konno and Mead (1968). This required the simultaneous recording of pressure (esophageal and gastric) and A-P diameter changes of the abdomen and rib cage. The relationship between A-P diameter and volume of each compartment was established by having subjects perform an isovolume manoeuvre, as well as breathe from a spirometer. The isovolume manoeuvre involved the subject alternating between abdominal and rib cage expansion with a closed glottis, thus maintaining a fixed lung volume. This procedure allowed a change in abdominal A-P diameter to be equated with a change in rib cage diameter. The relationship between both A-P diameters and volume was then established using spirometry.

Goldman and Mead (1973) attempted to show that the static characteristics of the rib cage were not influenced by a reduction in abdominal volume. In this study, the rib cage characteristics were measured under relaxed conditions with and without the inflation of a cuff around the abdomen. Inflation of the cuff resulted in a greater rib cage volume at a given esophageal pressure. The authors concluded that abdominal compression somehow imposed an expanding force on the rib cage. They proposed that this force originated in the diaphragm. The upward displacement of the abdomen due to inflation of the cuff stretched the diaphragm, creating the inspiratory force on the rib cage. If this proposal were correct, then the pressure imposed by the diaphragm would have to be subtracted from esophageal pressure to obtain the true pressure opposing motion of the rib cage. The authors tested their proposal by observing the relationship between rib cage volume and gastric pressure. They found that this relationship was not affected by inflation of the abdominal cuff, suggesting that abdominal pressure measured under relaxed static conditions could be used as an index of the recoil pressure of the chest wall, and that the characteristics of the chest wall were not influenced by abdominal displacement.

Goldman et al. (1976) measured the pressure-volume relationship for the rib cage and abdomen during both relaxation and exercise. Integration of the pressure-volume relationships resulted in a measure of the work of breathing, including that required for the chest wall distortion. Their measures of work using this approach are included in fig 11. This approach resulted in estimates of work approximately 30% greater than those made using the Campbell diagram approach (Margaria et al.1960; Milic-Emili et al.1962; Thoden et al.1969; Goldman et al.1976).

EXPIRATORY MUSCLES AND THEIR ROLE IN VENTILATION

DEFINITION AND DESCRIPTION OF THE EXPIRATORY MUSCLES

Expiratory muscle activity is reflected by P_{pl} becoming more positive than the recoil pressure of the chest wall at any V_L. There are two ways in which this can be achieved (fig 4). The first is to activate muscles within the chest wall which tend to decrease the thoracic volume thereby increasing P_{pl}. The second is to activate muscles external to the thorax but which will result in a positive pressure gradient across the chest wall. Muscle activity that will increase P_{ab} will result in pressure transmitted across the diaphragm and increase P_{pl}.

Campbell (1958) concluded that the intercostal muscles within the chest wall can act in an expiratory fashion but pointed out that there existed some controversy over which of the intercostal muscles (internal or external) are responsible. Based on geometric and electromyographic (EMG) information, it is currently believed that the external, parasternal internal and innermost intercostals are inspiratory in nature whereas the interosseous portion of the internal muscle is expiratory (Loring and De Troyer, 1985).

There are four major abdominal muscles that are capable of increasing abdominal pressure and therefore increasing P_{pl} and acting in an expiratory fashion. These muscles are:

External Oblique

This muscle originates from the outer surface of the lower 8 ribs runs medially and obliquely caudad to insert on the xiphoid process, the linea alba (forming a fibrous aponeurosis connecting it to the contra-lateral external oblique), and the pubic and iliac crests (Campbell, 1958; Snell, 1973). Thus, contraction of this muscle results in trunk flexion, depresses the ribs, as well as compressing the abdomen and increasing P_{ab}.

Internal Oblique

This muscle, oriented at right angles to the external oblique, originates from the lumbar fascia, the iliac crest and the inguinal ligament, runs medially and obliquely cephalad to insert onto the lower borders of the lower three ribs and costal cartilages, the xiphoid process and a fibrous aponeurosis similar to that of the external oblique (Campbell, 1958; Snell, 1973). Contraction of the internal intercostal results in flexion of the trunk, compression of the abdomen, as well as playing a minor role in depression of the ribs.

Transversus Abdominus

This muscle lies deep to the internal oblique, originates from the inner borders of the lower 6 ribs, the lumbar fascia, the iliac crest and the inguinal ligament, runs medially to insert on the xiphoid process, a fibrous aponeurosis along the linea alba, and the pubic symphysis (Campbell, 1958; Snell, 1973). Contraction of this muscle results in depression of the ribs and compression of the abdomen.

Rectus Abdominus

This muscle originates from the pubic symphysis and crest and runs vertically through a sheath between the aponeuroses of the oblique and transversus muscle to insert on the xiphoid process and costal cartilages of the 5th 6th and 7th ribs (Campbell, 1958; Snell, 1973). Contraction of the rectus abdominus results in flexion of the trunk as well as depression of the ribs.

Agostoni and Rahn (1960) measured gastric pressure (P_{ga}) as an index of P_{ab} and found that the capacity to generate pressure varied with V_L. A maximum voluntary contraction of the abdominal muscles produced P_{ga} of 120 cmH_2O at RV, 250

cmH_2O at FRC and 300 cmH_2O at TLC.

ELECTROMYOGRAPHIC ANALYSES OF EXPIRATORY MUSCLE

Campbell (1955) recorded the electrical activity of the intercostal muscles during hypercapnic hyperpnea with $\dot{V}_E$ of the order of 75 L/min and observed no activity during expiration. However, activity was observed at the onset and later stages of a maximal expiration from TLC to RV, as well as during static expiratory efforts greater than 30 cmH_2O. Campbell concluded that the intercostal muscles play a role in high pressure expiratory activity, but not during spontaneous ventilation, even at levels of $\dot{V}_E$ observed during heavy exercise.

Floyd and Silver (1950) recorded EMG activity from the rectus and oblique muscles during activities associated with the development of abdominal pressure. Electrical activity was observed during expulsive straining, head raising, coughing, singing, leg raising and postural adjustments (sitting down, standing up). Greatest activity was observed during leg raising and straining.

Campbell and Green recorded EMG in the rectus and oblique muscles as well as P_{ga} during hypercapnic hyperpnea in the supine and upright positions (Campbell and Green, 1953; Campbell and Green, 1955). These authors found that both P_{ga} and electrical activity increased during expiration at high levels of ventilation. Subjects in these studies were asked to voluntarily increase their $\dot{V}_E$ to the point that they felt no discomfort from the hypercapnia. The authors mentioned that the increase in electrical activity and P_{ga} during expiration might be a result of voluntary activity rather than a normal response to increased ventilatory demand (Campbell and Green, 1955). However, Strohl et al. (1981) observed increased EMG activity from the rectus muscle during hypercapnic hyperpnea where the subjects were not instructed to voluntarily increase their $\dot{V}_E$. The level of $\dot{V}_E$ at which EMG activity was first noticed varied between subjects from 18 to 56 L/min.

In the studies of Campbell and Green (1953; 1955) and Strohl et al. (1981) the electrical activity of the expiratory muscles was greater in the upright than supine positions. Druz and Sharp (1981) observed EMG activity of the oblique muscles even at rest in the upright but not supine position. They concluded that contraction of the abdominal muscles in the upright position occurred to elevate the abdominal contents, lengthening the diaphragm and optimizing its activity.

Naus (1989) has recorded surface EMG activity of the intercostal, internal and external oblique and rectus abdominus muscles during progressive upright cycling exercise. Activity of the internal and external oblique but not the rectus abdominus or intercostals was seen to be greater during expiration than inspiration. Furthermore, the level of activity during expiration increased with ventilation in these two muscles.

The EMG analyses of expiratory muscles indicate that they are active during increased ventilation. However, these analyses offer no insight into the function served by this activity.

VENTILATORY ROLE OF EXPIRATORY MUSCLE

The first potential role of the expiratory muscles is to support the inspiratory muscles by lowering of EELV to a point below FRC. The work performed by the expiratory muscles compressing the chest wall during expiration would be recovered during inspiration, reducing the load on the inspiratory muscles. Furthermore, a reduced EELV, would put the inspiratory muscles at a greater length and greater potential for developing inspiratory pressure. Another potential role served by the expiratory muscles is to generate pleural pressure such that expiratory flow exceeds that which could be achieved through passive recoil of the respiratory system alone. The evidence supporting these roles will be reviewed in the following sections.

Reducing EELV

Several studies have been made of the operating lung volume during exercise (table 1). The first measures of EELV during exercise were made by Asmussen and Christensen (1939), who had subjects perform maximal inspirations at the end of a normal expiration during cycle exercise, while measuring inspiratory capacity by simple spirometry. Change in EELV was reflected by the change in inspiratory capacity. Subjects exercised to 230 W and achieved ventilations of 65 L/min. EELV decreased progressively with exercise to a maximum of 1L (approximately 14 %TLC (Agostoni and Mead, 1964)) below resting level. The same technique has been used by other investigators (Lind and Hesser, 1984; Olafsson and Hyatt, 1969). Olafsson and Hyatt (1969) observed that EELV during exhaustive cycle exercise ($\dot{V}_E$ = 120 L/min) was 5 %TLC lower than at rest. Lind and Hesser (1984) had subjects exercise on a cycle ergometer up to 200 W ($\dot{V}_E$ = 60 L/min) and observed a progressive drop in EELV of 13 %TLC by 160W, after which there was no further drop.

Table 1 End Expiratory Lung Volume During Exercise

	Exercise	Technique	EELV Change
Asmussen ('39)	Cycle	Inspiratory Capacity	14%TLC by maximal exercise
Olafsson ('57)	Graded Walking	Inspiratory Capacity	↓ 5%TLC by maximal exercise
Younes ('84)	Cycle	Inspiratory Capacity	↓ 4%TLC at low WR No ↓ at maximal exercise
Lind ('84)	Cycle	Inspiratory Capacity	↓ 13%TLC by maximal exercise
Bouhuys ('55)	Leg Lifting	N_2 Washout	No change with mild exercise
Hanson ('59)	Walking	N_2 Washout	No change with mild exercise
Chiang ('60)	Walking	N_2 Washout	No change with mild exercise
Grimby ('51)	Cycle	Magneto-meter	↓ 11%TLC by 150W
Linnarson ('74)	Cycle	Magneto-meter	↓ 11%TLC by 240W
Kagawa ('70)	Cycle	Body Plethysmograph	↓ 4%TLC by 115W
Stubbing ('80)	Cycle	Body Plethysmograph	No change with 130W
Kiers ('80)	Cycle	He Dilution	↓ 5%TLC by 25W no ↓ at 125W
Sharrat ('87)	Cycle	He Dilution	↓ 13%TLC by 260W
Henke ('88)	Cycle	He Dilution	↓ 9%TLC by 230W
Johnson ('90)	Cycle	He Dilution	↓ 10%TLC by maximal exercise

Several investigators (Bouhuys et al.1956; Hanson et al.1962; Chiang et al.1965; Younes and Kivenen, 1984) have determined EELV during exercise using a N_2 dilution technique. This technique involves having the subject breathe from a closed volume of 100 $\%O_2$ and determining V_L based on the dilution of the N_2. Bouhuys et al. (1956), Hanson et al. (1962) and Chiang et al. (1965) used this technique on subjects performing mild exercise ($\dot{V}_E$ <30 L/min) in the upright position (walking (Hanson et al.1962; Chiang et al.1965); leg lifting (Bouhuys et al.1956)) and observed small (<3 %TLC) or no decrease in EELV. Younes and Kivenen (1984) employed this technique with subjects performing progressive WR cycle exercise until exhaustion ($\dot{V}_E$ = 81 at exhaustion). EELV decreased by 4 %TLC (statistically significant) at the lowest WR (37 W) and remained at that level until the maximum WR, at which point it returned to resting levels.

Helium dilution techniques have also been employed for determining EELV during exercise (Kiers et al.1980; Sharratt et al.1987; Henke et al.1988). This technique involves having the subject breathe from a closed volume containing a known [He] and determining V_L based on the magnitude of He dilution. Using this technique, Kiers et al. (1980) measured EELV in subjects cycling at WR up to 150 W ($\dot{V}_E$ = 50 L/min). They observed a 10% reduction in EELV (corresponding to approximately 5 %TLC (Agostoni and Mead, 1964)) at the lowest WR (25 W). However, as WR increased, EELV also increased, returning to resting levels by 125 W. In that study, the subjects began breathing from the known [He] at the end of a normal expiration. No mention is made as to how this was detected during exercise. Sharratt et al. (1987) also monitored EELV using He dilution during cycle exercise up to 260 W ($\dot{V}_E$ = 125 L/min) and observed a progressive decrease in volume as WR increased; at the maximum WR, EELV was 13 %TLC lower than at rest. In a similar study by these same authors (Henke et al. (1988)) EELV was seen to decrease by 9 %TLC during exercise at 230 W ($\dot{V}_E$ = 90 L/min). In both of these studies, connecting the subjects' airflow with the spirometer containing the known [He] was performed at the end of an expiration, based on inspection by the experimenter of a simultaneously displayed inductance plethysmograph signal.

Two studies have observed changes in EELV during exercise based on changes in abdominal and rib cage diameters, using linear transducers (Grimby et al.1968) and magnetometers (Linnarsson, 1974) attached to the surface of rib cage and abdomen. This requires correcting abdominal and rib cage diameter changes to correspond to lung volume changes, using the iso-volume procedure described earlier. Grimby et al. (1968) used this technique and found that EELV decreased by 14 %TLC during cycle exercise at 150 W ($\dot{V}_E$ = 83 L/min). Linnarsson (1974) observed a progressive decrease in EELV with increasing WR, to a level 0.75 L (approximately 11 %TLC) below that at rest, at a WR of 240 W ($\dot{V}_E$ = 80 L/min).

EELV has also been monitored during exercise using the body plethysmograph technique of DuBois et al. (1956). This technique requires that the subject be enclosed in the plethysmograph while performing ventilatory efforts against an occluded airway. Absolute lung volume is determined based on the degree of compression/expansion of the thoracic gas volume (detected through changes in plethysmograph pressure) for a given change in thoracic gas pressure (detected at the point of occlusion). Using this technique, Kagawa and Kerr (1970) measured a decrease in EELV of 3.7 %VC (approximately 3.0 %TLC (Agostoni and Mead, 1964)) during upright cycle exercise at 16 W and a decrease of 4.6 %VC (approximately 3.6 %TLC) at 115 W ($\dot{V}_E$ not reported). Stubbing et al. (1980) using a similar technique detected no change in EELV in subjects exercising to 130 W ($\dot{V}_E$ not reported). The response of EELV in this study may have been affected by the position of the subjects during the cycling exercise - sitting upright with their legs at a right angle to their trunk.

It has been suggested that the role of expiratory muscle is to support inspiratory muscle (Henke et al.1988; Grimby et al.1976; Forster and Pan, 1991). This would be achieved through the lowering of EELV, optimizing the length of inspiratory muscle and storing energy in elastic structures, for use during inspiration (Henke et al.1988; Grimby et al.1976; Forster and Pan, 1991). Several investigators have found little or no decrease in EELV with exercise (Hanson et al.1962; Chiang et al.1965; Stubbing et al.1980; Bouhuys et al.1956). Others have observed progressive decreases in EELV with WR but of varying magnitudes (Asmussen and Christensen, 1939; Grimby et al.1968; Kagawa and Kerr, 1970; Linnarsson, 1974; Lind and Hesser, 1984; Sharratt et al.1987; Henke et al.1988). Two studies have reported a decrease in EELV at low WR with a return to resting levels at moderate or high WR (Younes and Kivenen, 1984; Kiers et al.1980). Finally, during exhaustive exercise, a range of EELV have been reported, from unchanged to substantially lower than rest (Olafsson and Hyatt, 1969; Younes and Kivenen, 1984; Sharratt et al.1987; Henke et al.1988).

Increasing Expiratory Flow

Expiratory muscles can increase pleural pressure to values more positive than the recoil pressure of the chest wall. Margaria et al. (1960), Grimby et al. (1976) and Younes and Kivanen (1984) have measured P_{es} during moderate to heavy exercise to be greater than measures (Margaria et al.1960; Grimby et al.1976) or estimates (Younes and Kivenen, 1984) of $P_{el,w}$. Grimby et al. (1976) compared $P_{el,w}$ measured at rest with estimates of transpulmonary pressure (mouth pressure subtracted from P_{es}) made during 200W exercise. Their results indicate that transpulmonary pressure became equal to $P_{el,w}$ quite early in the expiration and exceeded $P_{el,w}$ by greater than 10 cmH_2O later in the expiration. These findings indicate that expiratory activity results in pleural pressures that should produce expiratory flow greater than could be achieved passively during exercise. The magnitude by which $P_{el,w}$ was exceeded indicates that the work performed through expiratory activity must be greater than 4% of total work of breathing (as was reported by Thoden et al. (1969)). Whether the increased pressure during expiration as a result of muscle activity actually produced increases in expiratory flow was not addressed in these studies (Margaria et al.1960; Grimby et al.1976; Younes and Kivenen, 1984).

Ollafsson and Hyatt (1969) attempted to determine whether expiratory activity remained effective (less than P_{maxeff}) during exercise. P_{pl} measured during exercise did not exceed P_{maxeff} measured at rest, indicating that expiratory activity remains effective during exercise. However, measures of P_{maxeff} made at rest may not reflect that occurring during exercise, as it is known that exercise may produce bronchodilation in normal subjects (Kagawa and Kerr, 1970).

Pleural pressure must at some stage of expiration lie in the shaded region of the Campbell diagram in fig 8 to generate increased expiratory flow. Despite all of these reported studies, in a recent publication, Forster and Pan (1991) suggest that the only role of the expiratory muscle is lowering EELV, and that decreased inspiratory braking throughout expiration is the means for increasing expiratory flow. Direct quantitative evidence linking pressure generated by expiratory muscle to increased expiratory flow is required.

PURPOSE OF PRESENT STUDIES

Clearly, the respiratory system has been well described using the classical techniques outlined here. It is somewhat surprising that these techniques have not been used to quantitatively describe the roles of expiratory muscles during exercise. The purpose of this thesis is to investigate the roles of the expiratory muscles during exercise. The primary hypothesis is that expiratory muscle activity will be important, both as a regulator of operating lung volume and as a contributor to expiratory flow. This hypothesis will be evaluated by answering the following questions:

1/ **Does expiratory activity during exercise result in a decrease in end-expiratory lung volume below the level of functional residual capacity?**

This will be investigated by measuring absolute V_L at several levels of exercise using tracer dilution, inductance plethysmography and the inspiratory capacity techniques.

2/ **Does expiratory activity during exercise result in a level of expiratory flow that could not be achieved through passive recoil of the lung and chest wall alone?**

This will be investigated by measuring expiratory P_{es} during exercise, comparing it to $P_{el,w}$, and relating any increases to simultaneous increases in expiratory flow.

3/ **Does expiratory activity remain effective at all levels of exercise?**

This has been investigated previously using resting measures of P_{maxeff} (Olafsson and Hyatt, 1969). Whether changes in P_{maxeff} influenced these results will be tested through repeated measures of pressure-volume and flow-volume loops during exhaustive high intensity exercise. Evidence that P_{es} increases at a given V_L without producing an increase in $\dot{V}_{exp}$ will be taken as an indication that P_{maxeff} has been exceeded.

4/ **What proportion of the total work of breathing is performed by expiratory muscle?**

Reports that expiratory work account for only 4% of total work of breathing with heavy exercise (Thoden et al.1969) seem unlikely given the magnitude by which $P_{el,w}$ is exceeded at these work rates (Margaria et al.1960; Grimby et al.1976; Younes and Kivenen, 1984). This will be investigated by calculating the total work of breathing, as well as that performed by the inspiratory and expiratory muscles.

5/ **What is the division of expiratory work between that lowering end-expiratory volume and that increasing expiratory flow?**

Authors have previously focused on lowering EELV below FRC as being the role of the expiratory muscles during exercise (Henke et al.1988; Grimby et al.1976; Forster and Pan, 1991). This will be investigated by comparing the work performed increasing $\dot{V}_{exp}$ to that performed lowering EELV.

A further aim of the thesis will be to determine whether breathing through a mouthpiece (as is usually required when measuring ventilatory mechanics) influences the findings from these investigations.

METHODS

INTRODUCTION

This chapter describes how measurements were made, processed and analyzed. Descriptions of the response characteristics of the equipment can be found in Appendix B.

SUBJECTS

Five healthy subjects were studied; descriptive characteristics are presented in table 2.

Table 2 Subject Characteristics

Subject	Sex	Age	Ht (cm)	Wt (kg)
MI	M	27	185	67
JI	M	29	183	70
KK	M	38	180	70
CK	M	31	185	84
JO	F	31	160	52

MEASUREMENT TECHNIQUES AND EQUIPMENT

PLEURAL, ABDOMINAL AND TRANSPULMONARY PRESSURE

Pleural pressure was approximated from esophageal pressure, measured using the balloon technique of Milic-Emili et al. (1964). This involved the nasal introduction and swallowing of an 11 cm latex balloon (A&E Medical Corp) at the end of a teflon catheter. The portion of the catheter contained within the balloon was perforated along its length to allow transmission of pressure. The balloon was initially placed so that its tip was 45 cm distal to the external nares. Adjustments in balloon position were then made until end-expiratory pressure was at its most negative, and cardiac artifact was minimal (Macklem, 1974). During measurement, the balloon was inflated with 0.5 ml of air, considerably less than the amount required for the balloon to develop pressure as a result of its elastic recoil.

Abdominal pressure was approximated from gastric pressure, measured using the balloon technique of Grimby et al. (1976). The balloon was identical to that used to measure P_{es} and was introduced in a similar manner except that it was placed 65 cm distal to the external nares. Gastric placement was confirmed by movement of the pressure signal in a positive direction during inspiration (Macklem, 1974).

Lines from both balloons were connected to pressure transducers (Hewlett-Packard, 267), the output signals of which were amplified (Hewlett-Packard, 8805A), yielding voltage signals proportional to P_{es} and P_{ga} (fig 12).

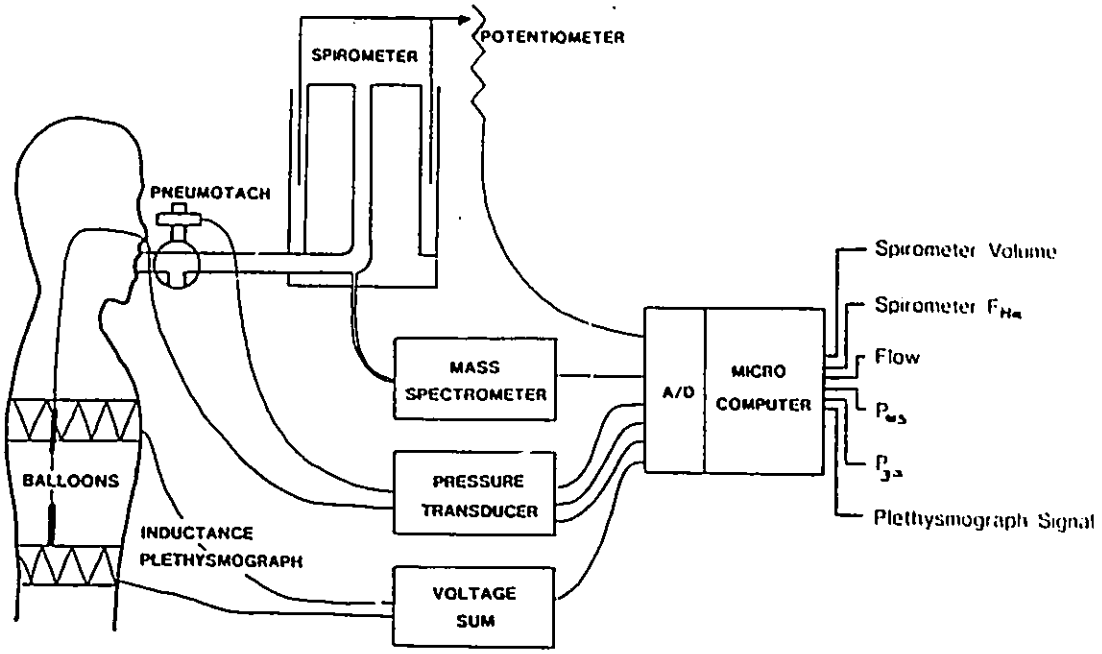


Fig 12 Equipment used in data collection. Signals listed on the right side of figure are those stored on computer during each testing session.

LUNG VOLUME

Lung volume was monitored using inductance plethysmography (Respitrace). This technique involved placement of two coiled wires around the subject, one at abdominal level (between iliac crest and twelfth rib) and one around the rib cage (nipple level). These coils were connected to a voltage oscillator, with the amplitude of the oscillations varying with the self inductance of the coil as a result of changes in the enclosed area (Sackner et al.1980). Voltage outputs proportional to the change in self inductance (and therefore enclosed area) of each coil, as well as their sum were amplified (Hewlett-Packard 8801C).

Absolute lung volume was measured using dilution of helium (Herrald and McMichael, 1939). Absolute lung volume was also inferred by subtraction of inspiratory capacity from TLC (measured). As both of these procedures were used in the calibration of the inductance plethysmograph signal, descriptions will be saved for the signal calibration section; discussion at this point will be limited to a description of equipment.

Measures of changes in lung volume for both techniques were made using a spirometer (Collin's, Modular Lung Analyzer). A linear potentiometer connected to the spirometer gave a voltage output proportional to the volume change (fig 12). Helium concentration within the spirometer was monitored via mass spectrometry (Perkin Elmer, MGA 1100) yielding a voltage output proportional to the gas fraction of Helium. A fan in the spirometer ensured that gases were well mixed.

INSPIRATORY/EXPIRATORY FLOW

In cases where subjects were breathing through a mouthpiece (on-mp), inspiratory and expiratory flow ($\dot{V}_{insp}$ and $\dot{V}_{exp}$) were measured via pneumotachometer (Fleisch) monitored by a differential pressure transducer (Hewlett Packard, 270) and amplified (8805A) to give a voltage signal proportional to $\dot{V}_{insp}$ and $\dot{V}_{exp}$ (fig 12). The pressure flow characteristics of the mouthpiece and pneumotachometer are illustrated in fig 13. In cases where the subject was breathing freely (off-mp), flow was calculated through differentiation of the plethysmograph signal (calibrated under each condition as described later).

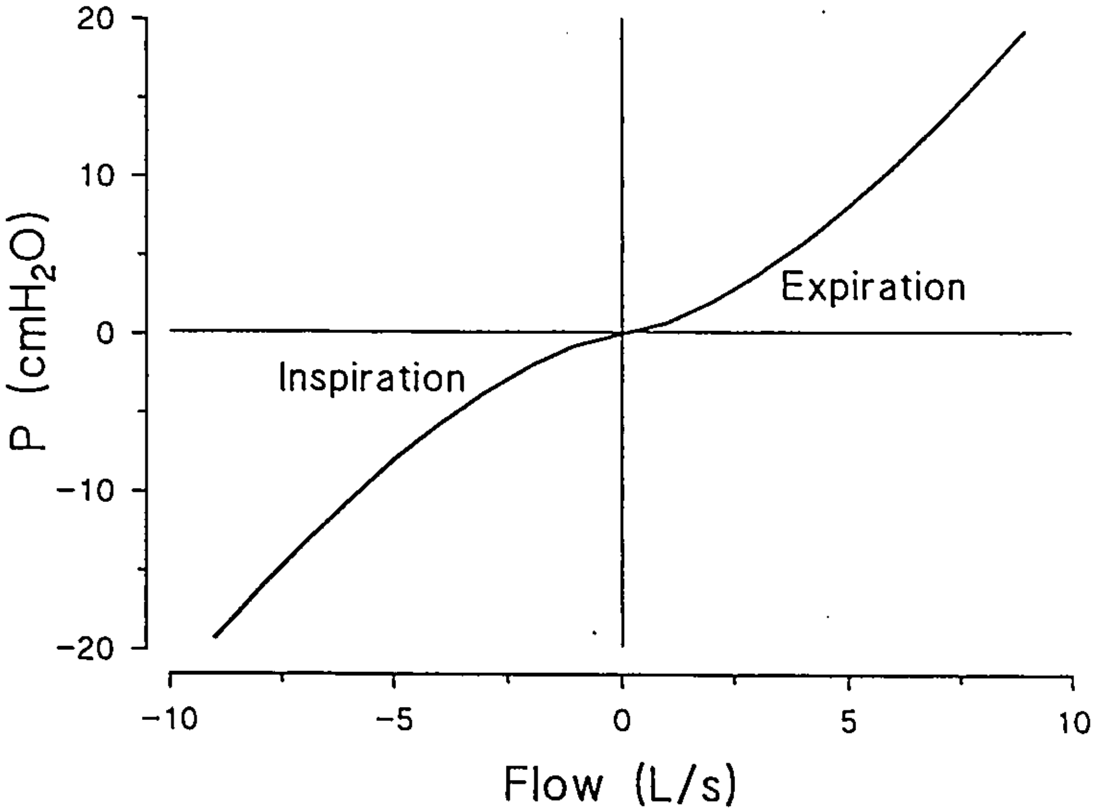


Fig 13 Pressure-flow characteristics of the mouthpiece and pneumotachometer.

VENTILATORY MEASURES

Minute ventilation ($\dot{V}_E$), tidal volume (V_T) and breathing frequency (*f*) were measured using open circuit gas exchange analysis (Sensormedics MMC Horizon metabolic cart). These variables were also measured under off-mouthpiece conditions through analysis of the summed plethysmograph signal. This technique is described in the analysis section.

SIGNAL RECORDING

All voltage signals were channelled through an analogue to digital (A/D) converter (Metrabyte, DASH16) and stored on a digital microcomputer (IBM PC portable) using a collection package (First Breath, Collect) (fig 12). All signals were sampled simultaneously at 32 Hz. At each sample time, values (A/D number) proportional to the voltage output of all measuring devices were stored on the computer hard disk.

SIGNAL CALIBRATION

As mentioned in the previous section, all values were stored as A/D numbers, this section describes how these numbers were converted to actual values. In all cases, except for the calibration of the inductance plethysmograph, calibration involved sampling A/D numbers corresponding to two known values for each signal. Regression equations between A/D numbers and known values yielded calibration factors for correcting all A/D numbers to real values. Calibration values were recorded prior to each test session.

PLEURAL AND GASTRIC PRESSURE

Esophageal and gastric balloons were calibrated using a water manometer while applying pressures over the range of -80 to 80 cmH_2O.

INSPIRATORY/EXPIRATORY FLOW

The pneumotachometer was calibrated by connecting it with a rotameter (F&P Co. Precision Bore Flowrator) and generating flows up to 8 L/s in each direction.

LUNG VOLUME

At the beginning of each study session, the subject performed an isovolume procedure required for calibrating the inductance plethysmograph (Konno and Mead, 1967). This involved shifting volume back and forth between the abdominal and rib cage compartments while maintaining a closed glottis. During this procedure, the gain of either the abdominal or rib cage plethysmograph coil was adjusted so that the voltage fluctuations of both coils were equal. Calibration of the inductance plethysmograph was achieved using two independent methods: helium dilution and TLC procedure. The inductance plethysmograph was calibrated using these techniques following all measures. Hence any change in position of the subject had little influence on the measurements.

Plethysmograph Calibration 1 - Helium Dilution

A modification of the helium dilution technique of Herrald and McMichael (1939) was used to calibrate the plethysmograph signal with respect to absolute lung volume. As this technique required the use of the spirometer/potentiometer and mass spectrometer, the procedures for their calibration will be outlined here.

The spirometer was calibrated by recording the voltage output from the potentiometer while adding gas from a 2L syringe. The signal from the mass spectrometer was calibrated by sampling two known concentrations of helium.

The process of the plethysmograph calibration is outlined in fig 14. Prior to the collection period, approximately 1000 mL of He was added to the spirometer, raising the F_{He} within the spirometer to roughly 12%. During the data collection period, approximately 4500 mL of O_2 was added to the spirometer, reducing the F_{He} to roughly 8%. The volume of the spirometer at this point was calculated based on the following equation:

$$V_{spir} = \Delta V\left(1 + \frac{F_2}{F_1 - F_2}\right) \tag{21}$$

where ΔV is the change in spirometer volume upon addition of the O_2 and F_1 and F_2 are the He fractions before and after adding the O_2. At the end of the collection period, a pneumatic switch was triggered (at a time corresponding approximately to end-expiration based on visual inspection of the summed plethysmograph signal), directing the subjects expiratory and inspiratory flow to and from the spirometer. The subject took one normal breath (CALIBRATION BREATH in fig 14) inspired to TLC, expired to RV, and then took 5 more deep breaths. This procedure resulted in a further dilution of the helium within the spirometer, allowing the subject's lung volume to be calculated based on the following equation:

$$V_L = V_{spir} \cdot \frac{F_2 - F_3}{F_3} \cdot \frac{273 + 37}{273 + T_r} \qquad (22)$$

where V_{spir} is that from equation (21), F_2 and F_3 are the helium fractions before and after the rebreathe procedure and T_r is room temperature. The second fraction in equation (22) corrects for the temperature difference between the spirometer and the subject. This correction is based on the assumption that the temperature in the spirometer did not depart from room temperature (T_r) during the rebreathe. This was confirmed by monitoring the spirometer temperature with a thermistor (Yellow Springs 43TA) during all rebreathes. Following this correction, the V_L measures corresponded to body temperature. pressure and water saturation (BTPS).

Knowing the V_L at the time of the switch into the spirometer allowed correction of the spirometer/potentiometer signal throughout the CALIBRATION BREATH so that it corresponded to absolute lung volume. The volume fluctuations in the spirometer/potentiometer signal were also corrected for temperature differences, so that the final signal corresponded to V_L (BTPS).

The inductance plethysmograph signal recorded throughout the collection period was corrected based on a regression between the corrected spirometer/potentiometer signal (corresponding to V_L - BTPS) and the plethysmograph signal made over the course of the CALIBRATION BREATH (see fig 14). Twelve points over the course of the CALIBRATION BREATH were used in the regression.

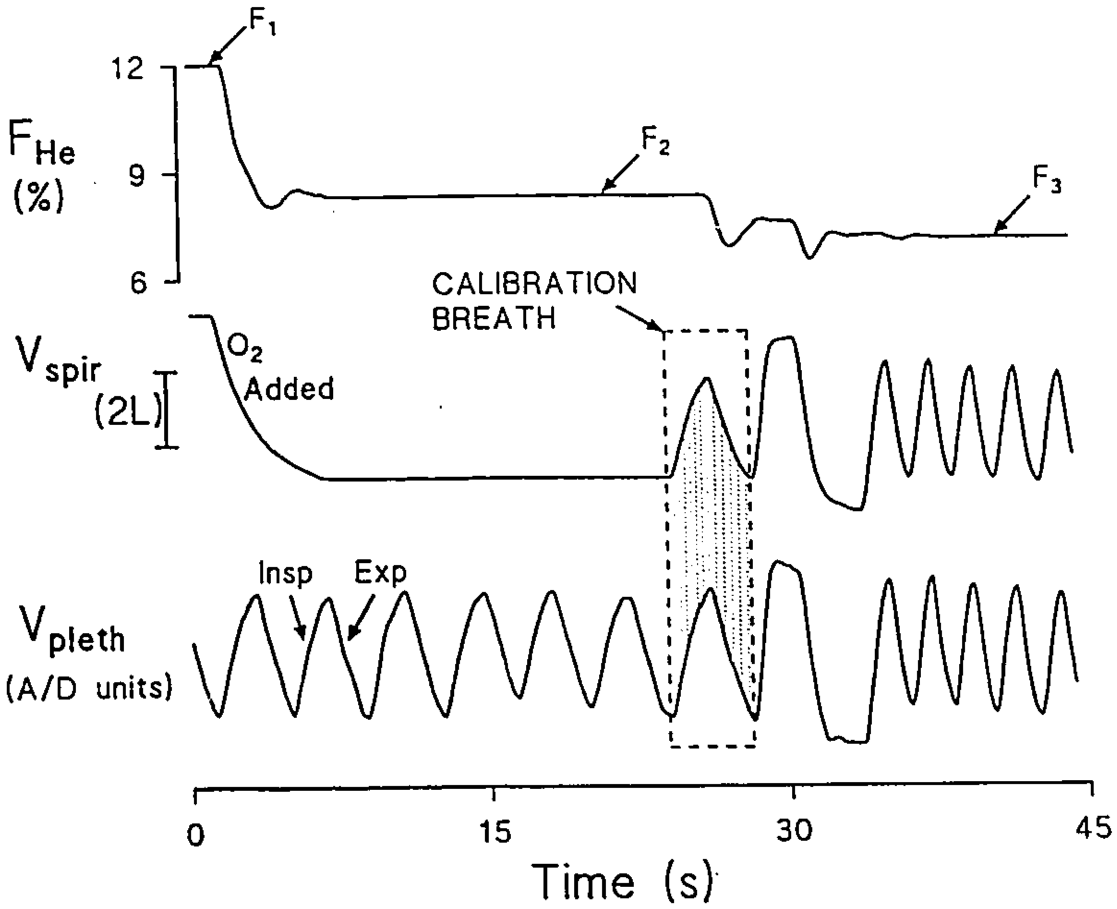


Fig 14 Helium dilution technique for calibrating the inductance plethysmograph. Signals represent fraction of He within spirometer (F_{He}), spirometer volume (V_{spir}), and summed signal from plethysmograph (V_{pleth}). F_1 and F_2 represent F_{He} before and after adding O_2 to spirometer. F_3 represents equilibration F_{He}, after subject has been breathing to and from spirometer. These values were used to calculate V_L at the point where the subject was connected to the spirometer (beginning of calibration breath). The V_{spir} signal was then corrected to represent V_L and then correlated with the V_{pleth} signal (dotted lines illustrate correlation points). The resulting regression equation was used to correct V_{pleth} to represent V_L.

Plethysmograph Calibration 2 - TLC Procedure

This technique was similar to the He dilution technique presented above, the difference being that an inspiratory procedure to TLC rather than helium dilution was used to determine absolute lung volume. The change in the gas volume of the spirometer between the point of switching in and the point of which maximum inspiration (corrected to BTPS) was subtracted from the subject's known TLC (measured at rest using helium dilution) to determine the absolute V_L (BTPS) at the point of switching in. Correction of the CALIBRATION BREATH and the plethysmograph signal were then carried out exactly as outlined in the description of the He rebreathe technique.

PROTOCOLS

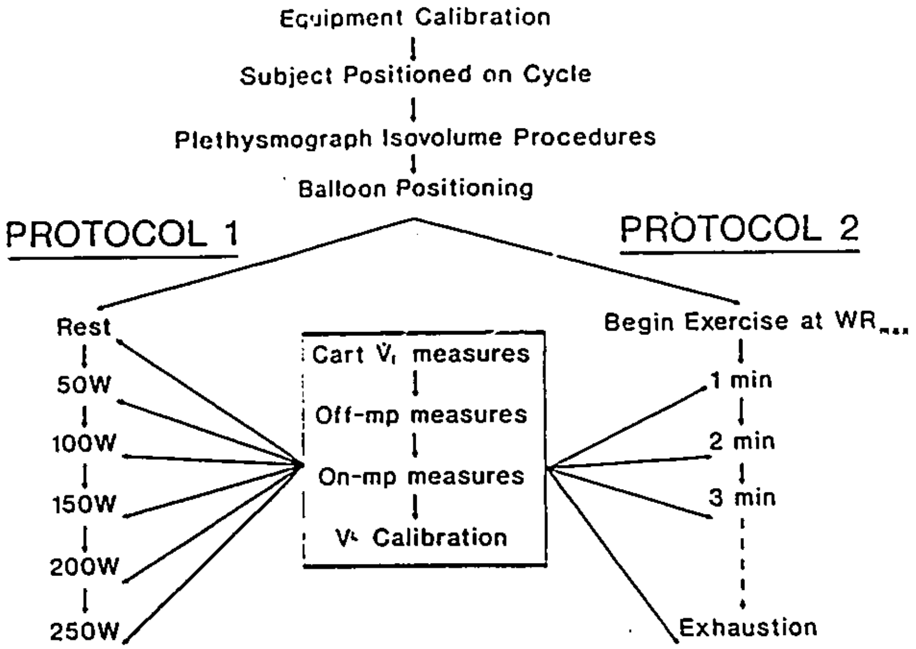
All subjects were studied during two different exercise protocols, performed on separate days. Both protocols involved the measurement of esophageal and gastric pressure, lung volume and flow under varying conditions of cycle ergometry exercise and involved the following steps:

1. Equipment calibration.
2. Plethysmograph coil attachment and isovolume procedure (performed with subject seated on ergometer in same position as during exercise).
3. Swallowing and positioning of balloons.
4. Beginning of exercise.

5. Under a specific condition (ie work rate, duration) data collection began.
   a. First half of each collection period was with subject breathing freely, but positioned such that the mouth was within two inches of the mouthpiece (noseclips were worn).
   b. Second half of each collection period was with subject breathing through mouthpiece. Subjects were instructed to change their posture as little as possible when going on to the mouthpiece.
6. Immediately following every collection period, both methods for calibrating the plethysmograph (helium dilution and TLC procedure) were performed simultaneously.
7. Steps 5 and 6 were repeated under all experimental conditions.

PROTOCOL 1

Following an initial set up procedure as described above, subjects were monitored at rest and during 50W increments of exercise up to 250W according to the outline in fig 15. Subjects exercised at each work rate for 4 minutes prior to the off-mp recording. Direct ventilatory measures were made during the minute prior to off-mp recording. The female subject followed the same protocol but exercised in 40W increments up to 200W.



<u>Fig 15</u> Outline of protocols 1 and 2. Events listed in central box were preformed repeatedly throughout both protocols as indicated. Thus, the plethysmograph was calibrated (V_L calibration) following each data collection period. Ventilatory measure were not made during protocol 2.

PROTOCOL 2

Prior to beginning protocol 2, subjects were required to perform a progressive exercise test to exhaustion (on a separate day). This involved exercising on the cycle ergometer while the work rate was increased by 20W each minute. The last work rate which the subject could maintain for the full minute was chosen as that to be used for protocol 2 and will be referred to as WR_{max}.

During the subject preparation for protocol 2, care was taken to ensure that balloon placement was the same as for protocol 1. Following the initial set up, subjects began riding at WR_{max} and collections were made approximately every minute according to the outline in fig 15. Exercise under this protocol continued until the subject was exhausted, with the final collection being taken as the one before the last complete calibration procedure. Direct measures of ventilation were not made during this protocol.

Maximal dynamic inspiratory and expiratory pressures and flows at maximal exercise were also measured during this protocol. This involved each subject performing a maximal expiratory effort, from TLC to RV followed by a maximal inspiratory effort to TLC. This was done immediately following the CALIBRATION BREATH illustrated in fig 14, after the final collection period (ie. just prior to the cessation of exercise). V_L (via the spirometer/potentiometer signal) and P_{es} were recorded throughout these expiratory and inspiratory efforts.

ANALYSES

AVERAGING OF BREATHING CYCLES

Two techniques were used to average breathing cycles. Within-subject averaging was used to calculate breathing cycles representing the mean response of a single subject under a given condition. Between-subject averaging was used to calculate breathing cycles representing the mean response of all subjects under a given condition. Both of these techniques are described here and illustrated in Appendix C. The basic programs written to perform this averaging can be found in Appendix A.

Within-subject Averaging

Within-subject averages represent the mean of three consecutive breaths taken under a given condition. These breaths were usually the last three recorded breaths under that condition; exceptions were made when any signal at this point was excessively noisy (eg. due to subject movement, swallowing etc.). The V_L (calibrated plethysmograph), $\dot{V}_L$ (pneumotachometer), P_{es} and P_{ga} signals recorded during the three breaths were each divided into 6 sections, three inspirations and three expirations. The three inspiratory data sets were combined, sorted according to lung volume and averaged such that three data points were reduced to one. The time signal of the resulting inspiration was adjusted so that it corresponded to the average inspiratory time of the three breaths. After the same procedure was applied to the expiratory segments, the averaged inspiration and expiration were combined, resulting in an average breathing cycle.

Between-subject Averaging

Between-subject averages represent the mean breathing cycle for all subjects under a given condition. These were calculated using all subject's within-subject average cycle from that condition. These within-subject average cycles were divided into 40 time periods (20 equal periods throughout inspiration and 20 throughout expiration). All data points within each time period were averaged, resulting in a breathing cycle described by 40 points. The 40 point data sets for all subjects were combined and averaged, resulting in one 40 point data set representing the mean response of all subjects.

PLURAL PRESSURE UNDER STATIC CONDITIONS

The pleural pressure required to overcome the elastic recoil of the lung was determined using the technique of Knowles et al. (1959). Measurements were made with subjects at rest, seated on the cycle ergometer prior to performing protocol 1. With the esophageal balloon in place, the subject was connected with the spirometer and a He dilution procedure was performed to determine V_L. During the He dilution procedure, the subject exhaled to RV and then inhaled with a slow regular flow rate (less than 0.2L/s), taking at least 15s to reach TLC. The P_{es} and V_L records of this procedure were divided into 10 equal segments by volume and averaged, yielding 10 pressure and volume values describing the $P_{pl\text{-}stat}$ curve. As this curve was constructed with measures of esophageal rather than true pleural pressure, it will be referred to as $P_{es\text{-}stat}$. For the purpose of measuring the work of breathing, the dynamic compliance technique for measuring the $P_{es\text{-}stat}$ curve was also used. In this technique, the esophageal pressure measured at end-inspiratory and end-expiratory lung volumes (ie when no flow was taking place) was taken as the pressure required to overcome lung recoil at that particular lung volume ($P_{es\text{-}stat}$). By recording end-inspiratory and end-expiratory pressures at each exercise level in protocol 1 (and thus at a variety of end-inspiratory and end-expiratory lung volumes) it was possible to generate a curve describing $P_{es\text{-}stat}$ over a range of V_L.

CHEST WALL RECOIL CURVES

The recoil pressure of the chest wall was estimated using the data of Knowles et al. (1959). This estimation was tested by measuring the chest wall recoil in two subjects.

The data published by Knowles et al. (1959) are in the form of a curve plotting lung volume as % vital capacity against chest wall recoil pressure. The shape of this curve was used to estimate chest wall recoil in the present studies. The actual position of the curve was determined by each subjects resting end-expiratory pressure and volume. This procedure is illustrated in fig 16.

Measures of chest wall recoil pressures were made from two subjects using the technique of Knowles et al. (1959). This involved having the subjects inhale or exhale a volume of air and then attempt to relax their respiratory muscles while airflow was occluded and esophageal pressure measured. The esophageal pressure was taken as the recoil pressure of the chest wall. The corresponding lung volume was determined immediately following each relaxation procedure by switching the subjects airflow into the spirometer and performing a helium dilution. In an attempt to facilitate relaxation during this procedure, subjects were asked to take several deep rapid breaths prior to each measure.

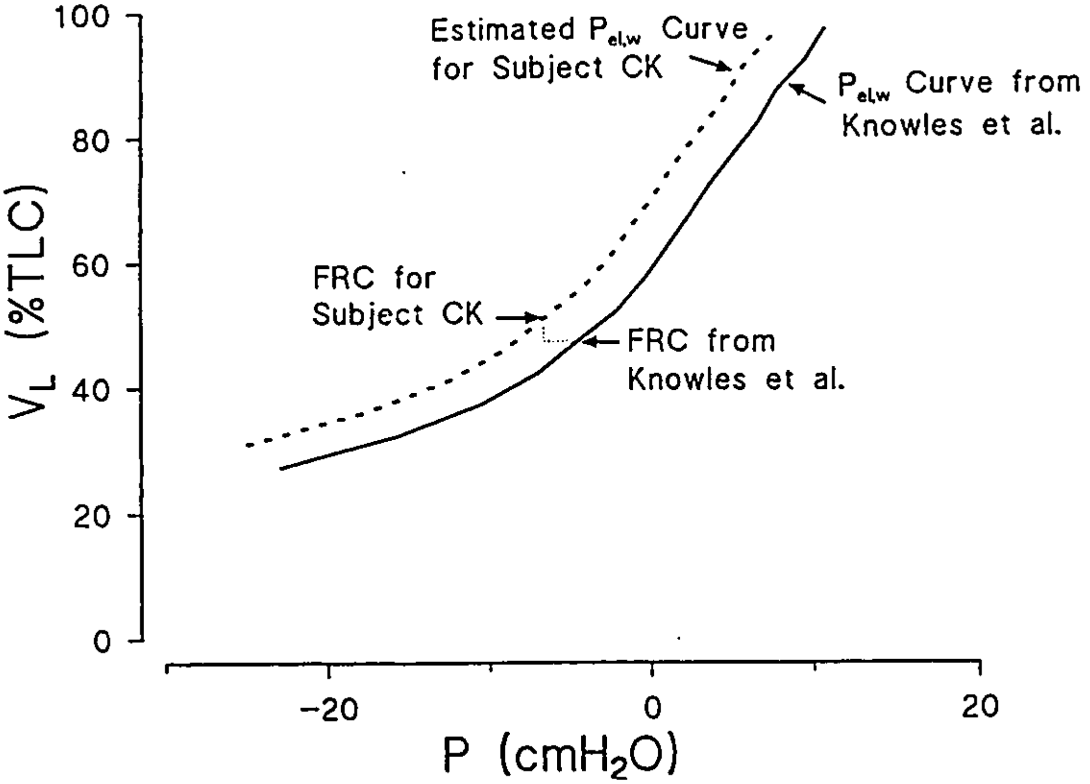


Fig 16 Method for estimating $P_{el,w}$ curve based on measures made by Knowles et al. (1959). The solid curve is that presented by Knowles et al. (1959). This curve was repositioned, so that the point corresponding to resting end-expiratory lung volume (labelled FRC) was at the same point as the measured resting EELV for the subject.

MAXIMAL DYNAMIC PRESSURE AND FLOW-VOLUME RECORDS

Records of V_L and P_{es} were obtained during the maximal expiratory and inspiratory efforts made during maximal exercise. The V_L signal was differentiated with respect to time, resulting in a flow signal.

As V_L was measured from the spirometer signal, rather than the plethysmograph, it was necessary to correct for compression and expansion of the thoracic gas (owing to the large positive and negative alveolar pressures during these maximal efforts). An approximation of the alveolar pressure throughout these maximal dynamic efforts was obtained by subtracting each subject's $P_{es\text{-}stat}$ at the appropriate V_L from each point on the P_{es} record.

The V_L, P_{es} and flow signals were averaged exactly as already described, resulting in between-subject average pressure and flow-volume relationships describing maximal dynamic efforts under maximal exercise conditions.

WORK OF BREATHING

Work of breathing was calculated according to the pressure-volume integration method described in the introduction and illustrated in fig 10. Calculation of work using this method requires a dynamic pressure-volume relationship throughout the breathing cycle, knowledge of the pleural pressure required to overcome the recoil of the lung ($P_{pl\text{-}stat}$), the contribution to pleural pressure by the static recoil of the chest wall ($P_{el,w}$), and the resistive properties of the chest wall (R_w).

Measures of P_{es} and V_L from the within-subject average breathing cycles were used to describe the dynamic pressure-volume relationships. The curves describing the $P_{pl\text{-}stat}$ and $P_{el,w}$ were obtained as described above (the dynamic compliance technique used for determining $P_{es\text{-}stat}$ was used as an indicator of $P_{pl\text{-}stat}$). In cases where the subject was breathing through the mouthpiece, the pressure required to overcome the resistance of the mouthpiece and pneumotachometer was subtracted from P_{pl} before calculating work.

The resistance of the chest wall was estimated using equation (17), or taken to be 0.49 cmH$_2$O/L/s, whichever was higher. This value was then multiplied by flow to determine the pressure required to overcome R_w at any given time during the breathing cycle.

A basic program was written to calculate the areas illustrated in fig 10 and thus calculate the different components of both inspiratory and expiratory work of breathing. This program, included in Appendix A was iterative and involved dividing the pressure-volume loop into 100 horizontal strips (the height of each strip being equal to 1/100 of tidal volume). The area of each strip that was contained in any given specific area from fig 10 was calculated by subtracting the magnitude (pressure) of the curve bordering the right side of that specific area from the magnitude of the curve bordering the left side and multiplying by $V_T/100$. For example, area G in fig 10 (work done during inspiration by chest wall recoil on chest wall resistance) is bordered on the right by the chest wall resistance curve or the inspiratory P_{pl} curve (depending on which is more negative) while on the left it is bordered by the E_w curve. Once the 100 inspiratory and 100 expiratory iterations were complete, the calculated areas were summed, giving the total area of each of the 18 specific work areas illustrated in fig 10. These areas represented the work done per breathing cycle. Each work value was multiplied by the breathing frequency to give power in $cmH_2O \cdot L/min$ and then divided by 100 to give power in kpm/min.

To calculate the total muscular work of breathing, all areas representing work performed by inspiratory or expiratory muscle were summed (ie areas A,B,C,D,H,I,J,K,Q and R in fig 10). Total inspiratory work was calculated by summing the areas representing the positive (areas A,B,C and D in fig 10) and negative (area Q and R in fig 10) work. Total expiratory work was calculated by summing the areas representing the positive (areas I,J and K in fig 10) and negative (area H in fig 10) work. The work performed by expiratory muscles was further divided into total resistive (areas J and K in fig 10) and elastic work (area I in fig 10).

The work of breathing calculated using the technique described here does not account for any work performed in the distortion of the chest wall. The reason for this will be presented in the discussion section.

VENTILATORY MEASURES

The calibrated plethysmograph signal was analyzed to determine $\dot{V}_E$, V_T and f. Tidal volume was calculated as the average difference between end-expiratory and end-inspiratory volume on the plethysmograph signal during each on-mp and off-mp recording. Breathing frequency was calculated using the number of breaths recorded during each on-mp and off-mp recording, and converted to breaths/minute. Minute ventilation was calculated as the product of V_T and f.

STATISTICAL ANALYSES

All comparisons between groups of means were made using multiple analyses of variance with a repeated measures design (ANOVA_{rm}) (Keppel, 1982). Allowing for heterogeneity of variance, all F values were compared to Geiser-Greenhouse corrected critical values of F at an $\alpha = 0.05$ level (Keppel, 1982). Post hoc analyses following significant main effects were made using Newman-Keuls corrections for family wise error (Keppel, 1982). To allow for heterogeneity of variance, the error term for these post hoc tests was generated using only the data within the cells included in the comparison (Keppel, 1982).

RESULTS AND DISCUSSION

EVALUATION OF MEASUREMENT/CALIBRATION TECHNIQUES

INDUCTANCE PLETHYSMOGRAPHY AS AN INDEX OF LUNG VOLUME AND VENTILATORY FLOW RATE

Calibration of the inductance plethysmograph signal required the initial measurement of absolute lung volume, and calculation of a regression equation relating the summed plethysmograph signal to the simultaneous spirometric recording. The correlation coefficients from these regressions are presented in table 3. Fig 17 shows simultaneously recorded plethysmograph and spirometer signals from all subjects during the final CALIBRATION breath at WR_{max}. The plethysmograph signal in this figure has been corrected based on the linear regression and absolute lung volume measurement. Hence, the summed plethysmograph signal may be used as an index of V_L during cycling exercise when calibrated in this way.

Table 3 Coefficients from correlation between plethysmograph and spirometer signals.

	WR	rest	50	100	150	200	250	WR_{max}
r^2		0.992	0.993	0.994	0.989	0.980	0.982	0.979
(SE)		0.002	0.001	0.002	0.004	0.003	0.004	0.006

While subjects were exercising off-mouthpiece, the first derivative of the inductance plethysmograph signal was used as an index of $\dot{V}_L$. To estimate the validity of this technique, a comparison was made between the first derivative of the plethysmograph signal and a simultaneous record from the pneumotachometer under on-mp conditions. Fig 18 illustrates this comparison for all subjects during maximal exercise. Although flow, calculated through differentiation of the plethysmograph signal is not identical to the simultaneous pneumotachometer measure, a close approximation is evident.

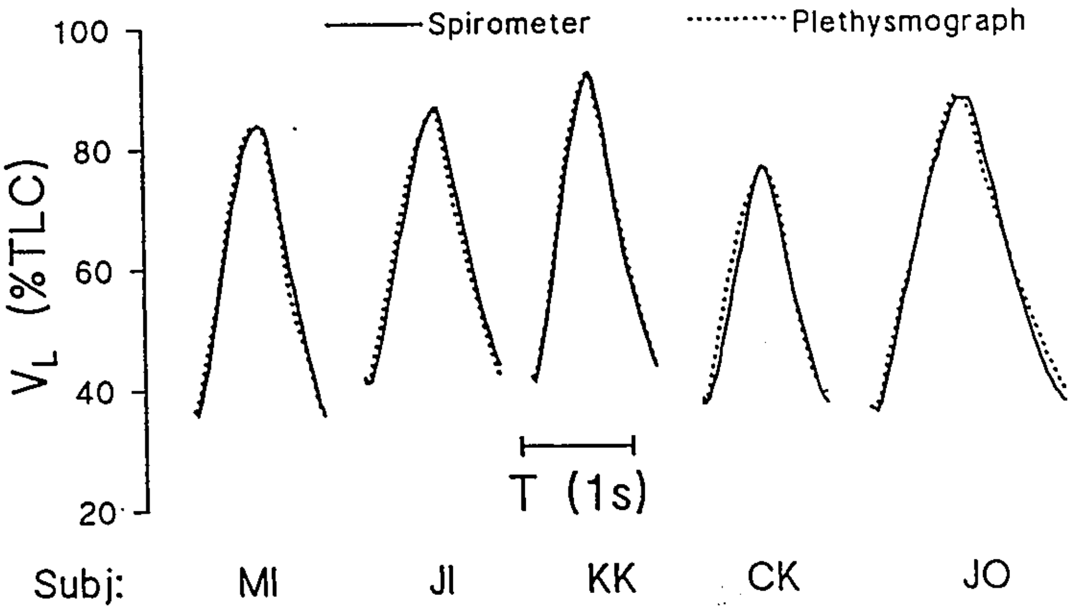


Fig 17 Simultaneous recordings of spirometer and inductance plethysmograph signals at WR_{max}.

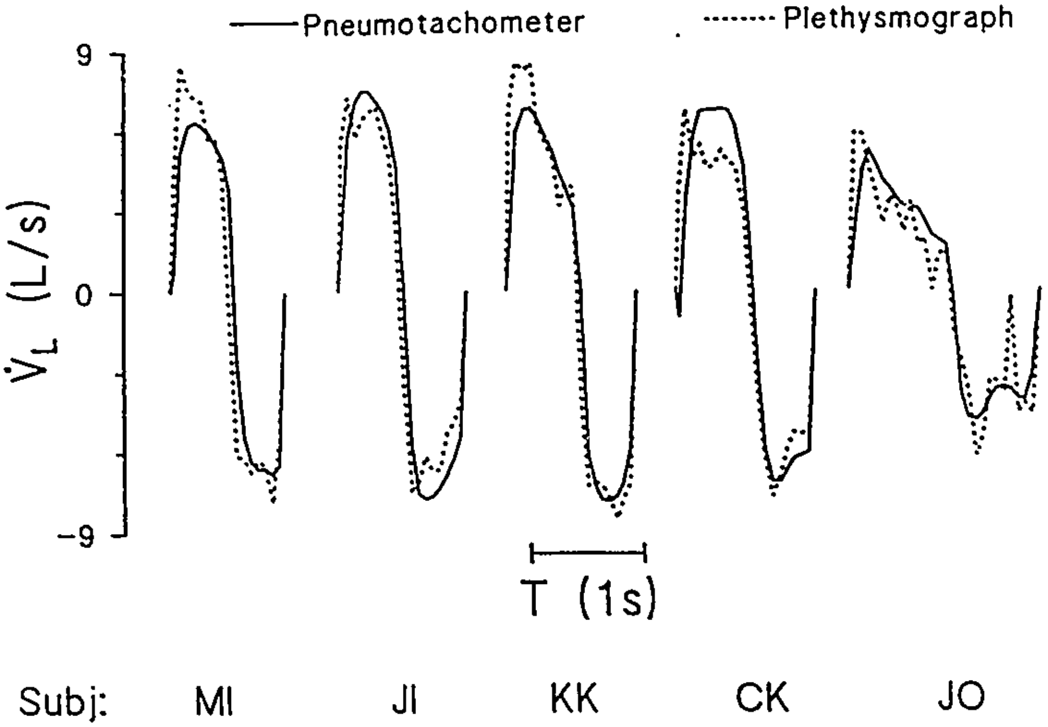


Fig 18 Simultaneous tracings of pneumotachometer signal and first derivative of inductance plethysmograph signal at WR_{max}.

Discussion

Impedance plethysmography was developed as a non-invasive tool for monitoring changes in lung volume (Sackner et al.1980). The technique is based on the idea that changes in the volume of the lung wall should be equal to the sum of changes in the volumes of the abdomen and rib cage, and that these changes may be determined using surface measures (Konno and Mead, 1967). Initial attempts to indirectly determine changes in rib cage and abdominal volume were based on changes in anterior to posterior diameter, measured using linear transducers (Konno and Mead, 1967; Grimby et al.1968; Konno and Mead, 1968; Goldman and Mead, 1973) or magnetometers (Grimby et al.1976; Goldman et al.1976) attached to the body surface. The inductance plethysmograph signal measures changes in the cross-sectional area, and should provide a closer approximation of changes in the volume of each compartment (Sackner et al.1980; Konno and Mead, 1967). As used in the present study, the summed inductance plethysmograph signal accurately estimates changes in lung volume over the range of volumes observed from rest to maximal exercise. Although previous reports have suggested that the inductance plethysmograph can be used to monitor lung volume during exercise (Sackner et al.1980), when compared to a tracer gas dilution technique, it has been shown to be unreliable and inaccurate in this setting (Sharratt et al.1987). Based on these results, impedance plethysmography was used in the current study only as a means of measuring changes in lung volume throughout the breathing cycle, He dilution was used at each exercise level to determine absolute lung volume.

HELIUM DILUTION vs TLC CALIBRATION PROCEDURES

The He dilution and TLC methods (TLC - inspiratory capacity) were used to calibrate the inductance plethysmograph signal during the progressive exercise study. A comparison between these two techniques was made by simultaneously determining each subject's EELV at each protocol 1 exercise WR, using both calibrations. The EELV for comparison represents the average from the three breaths prior to the switch into the spirometer during the on-mouthpiece collection period. Fig 19 is a plot of the mean EELV measured during all exercise WR using both calibrations. At all exercise levels the TLC calibration method resulted in a higher value for EELV than the He dilution method. Although this difference was small (0.16 ± 0.08 L at 250 W, representing 2.3 ± 1.2% TLC) an $ANOVA_{rm}$ showed it to be statistically significant ($p < 0.05$). This difference of 0.16L at 250 W is almost identical to the difference of 0.15L observed by Johnson et al. (1990) when they compared He dilution and TLC procedures for determining EELV at maximal exercise.

The reason for the small difference in V_L measures using the two calibration techniques is not known. It is possible that during exercise, subjects did not inspire completely to TLC. This would have resulted in falsely high V_L values following the TLC method for calibrating the plethysmograph signal.

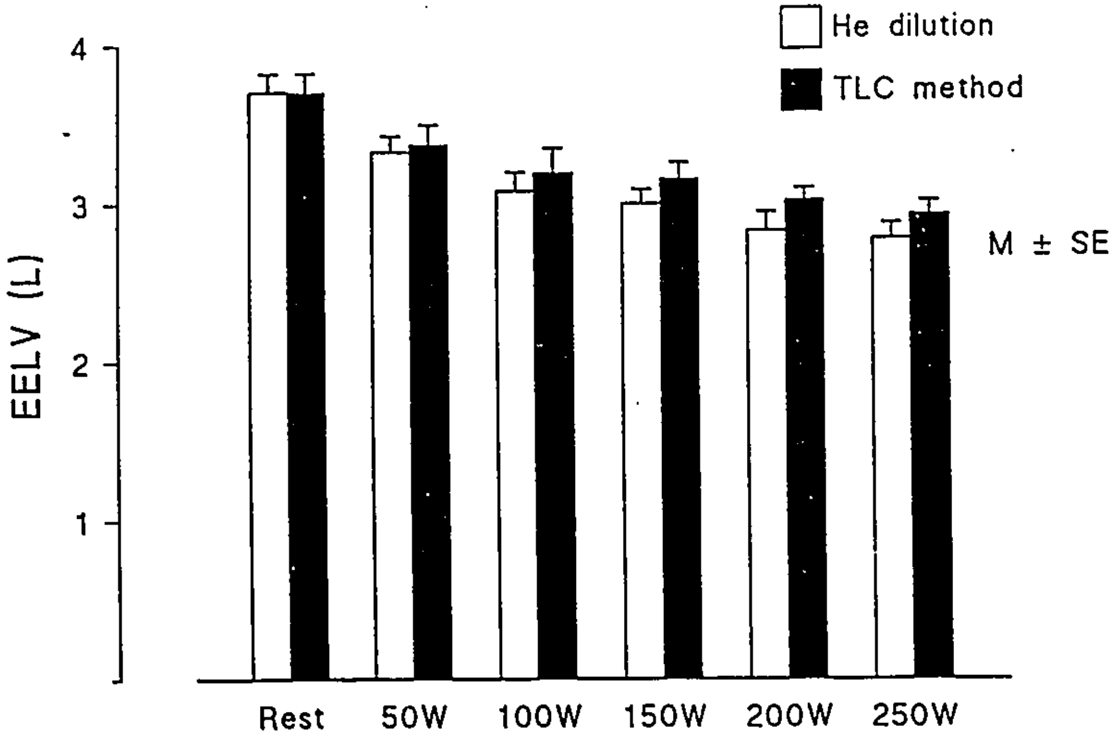


Fig 19 A comparison between EELV determined using the He dilution and TLC calibration procedures.

V_L was determined using the dilution of a single tracer gas (He). It has been suggested that differences in the exchange rates for O_2 and CO_2 (RER-effect) would result in volume changes in the lung spirometer system during the rebreathe (Johnson et al.1990; Nunnely et al.1974; Boutellier and Farhi, 1986). These authors suggest that the dilution of nitrogen plus an inert gas be measured to calculate V_L during exercise, so that the RER-effect will not influence V_L measures. In appendix D, the magnitude of the R-effect on V_L determination was investigated. The results show that at rest (where gas exchange is relatively small) and at maximal exercise (where the ratio of CO_2 output to O_2 intake - RER is close to 1), the error in V_L determination is approximately 0.5%. Between these extremes, the error increases, but only reaches a maximum of 2.0% (equivalent to 0.96% of TLC) at 150W.

Despite the statistically significant difference in EELV measures based on the two calibration techniques, the difference (2.3 %TLC) is small. Thus, the use of either of these techniques in previous investigations (He rebreathe - (Kiers et al.1980; Sharratt et al.1987; Henke et al.1988); TLC procedure - (Asmussen and Christensen, 1939; Olafsson and Hyatt, 1969; Stubbing et al.1980; Younes and Kivenen, 1984; Lind and Hesser, 1984) seems appropriate. The results presented in the remainder of this thesis are based on the He dilution technique.

MEASURED vs ESTIMATED $P_{el,w}$

The curve describing the pressure from chest wall recoil ($P_{el,w}$) was estimated based on mean relaxation pressures of Knowles et al. (1959), and was also measured in two subjects using the same technique as Knowles et al. (1959). In fig 20, these measured $P_{el,w}$ curves are compared to estimations. For both subjects, esophageal pressure measured during relaxation was close to the curve of Knowles et al. (1959) at all lung volumes. Given the variability in the relaxation pressure measures, it does not appear that measuring the $P_{el,w}$ curve in every subject would have resulted in a higher degree of accuracy than obtained using the estimation.

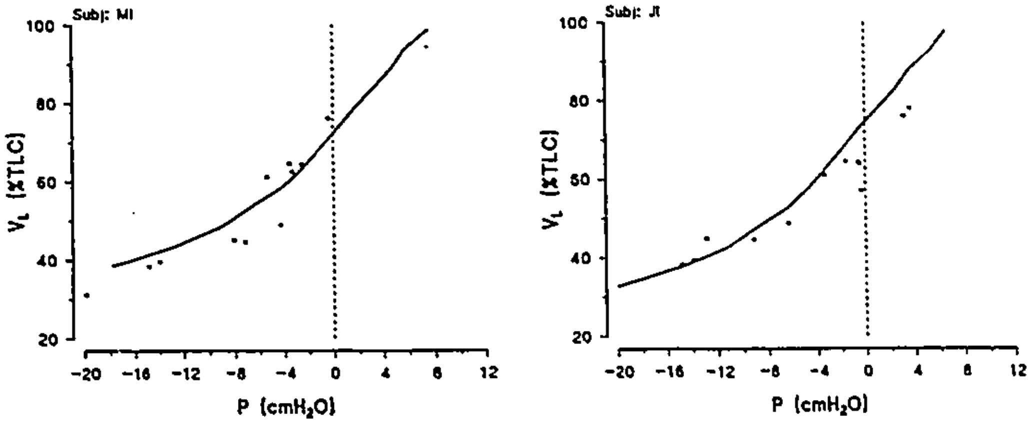


Fig 20 Comparison between measured and estimated $P_{el,W}$ in two subjects. The curved line represents the estimated $P_{el,W}$ based on measures made by Knowles et al. (1959). Points represent individual measures of P_{es} during relaxation.

MAXIMUM WORK RATE TEST

The WR achieved by each subject during the progressive exercise test is presented in table 4. Also included in table 4 is the length of time for which each subject was able to continue exercising at WR_{max} during protocol 2.

Table 4 WR_{max} and time to exhaustion ($T_{exhaust}$) during protocol 2 test.

Subject	WR_{max} (W)	$T_{exhaust}$ (min)
MI	320	5:00
JI	270	4:00
KK	275	4:00
CK	250	6:00
JO	215	4:00

VENTILATORY RESPONSE TO EXERCISE

Minute ventilation, tidal volume and breathing frequency were measured at each WR throughout protocol 1 using direct measurement and using the plethysmograph tracing calibrated as described. The mean values of these measures are presented in fig 21. An $ANOVA_{rm}$ showed no significant differences between direct and plethysmograph measures (all p's > 0.05). Although the $ANOVA_{rm}$ showed no significant difference, fig 21 indicates a difference between the direct and plethysmograph measures of $\dot{V}_E$ at 250W. A paired t-test analysis of the $\dot{V}_E$ data at 250W indicated a significant difference, with plethysmograph measures being greater than direct measures ($p < 0.05$). This difference is likely owing to the fact that direct measures were made approximately 1 minute earlier than plethysmograph measures. At this level of exercise, one would expect $\dot{V}_E$ to increase continually with time (95).

Comparisons were also made between on and off-mp ventilatory measures. Plethysmograph determinations of $\dot{V}_E$, V_T, and f made under on and off-mp conditions are presented in fig 22. The WR_{max} values presented in this figure are those measured during the final minute of exercise during protocol 2. An $ANOVA_{rm}$ showed no significant differences between on and off-mp measures of any variables (all p's > 0.05).

These findings do not indicate differences between on and off-mp $\dot{V}_E$, V_T or f during exercise. Sackner et al. (#95) and Henke et al. (#1) have also measured ventilatory variables using inductance plethysmography during off-mp exercise. Sackner et al. (#95) found that $\dot{V}_E$ was 24% greater when breathing through a mouthpiece with 150mL added dead space and nose clips than when breathing freely during 130W cycling exercise. This increase was almost entirely owing to an increase in *f*. Henke et al. (#1) however did not observe any significant effect of mouthpiece breathing on measures of $\dot{V}_E$, V_T, or breathing pattern except at near maximal exercise, where V_T was 3.2% greater while breathing on-mp.

The reason for the differences between the findings of Sackner et al. (#95) and the findings of Henke et al. (#1) and the current studies is not clear. It is possible that postural changes during the study of Sackner et al. (#95) may have influenced their measures. No mention is made of fixing postural position between on and off-mp measures as was done in the current study and that of Henke et al. (#1). Another source of possible error in the Sackner et al. (#95) study was that calibration of the plethysmograph was only performed at rest, possibly resulting in errors in exercise measures. Lastly, the protocols for the studies were different; Sackner et al. (#95) had subjects breathe off-mp for the duration of exercise, whereas subjects in the current study, and that of Henke et al (#1) came off the mouthpiece only to make the required measurements.

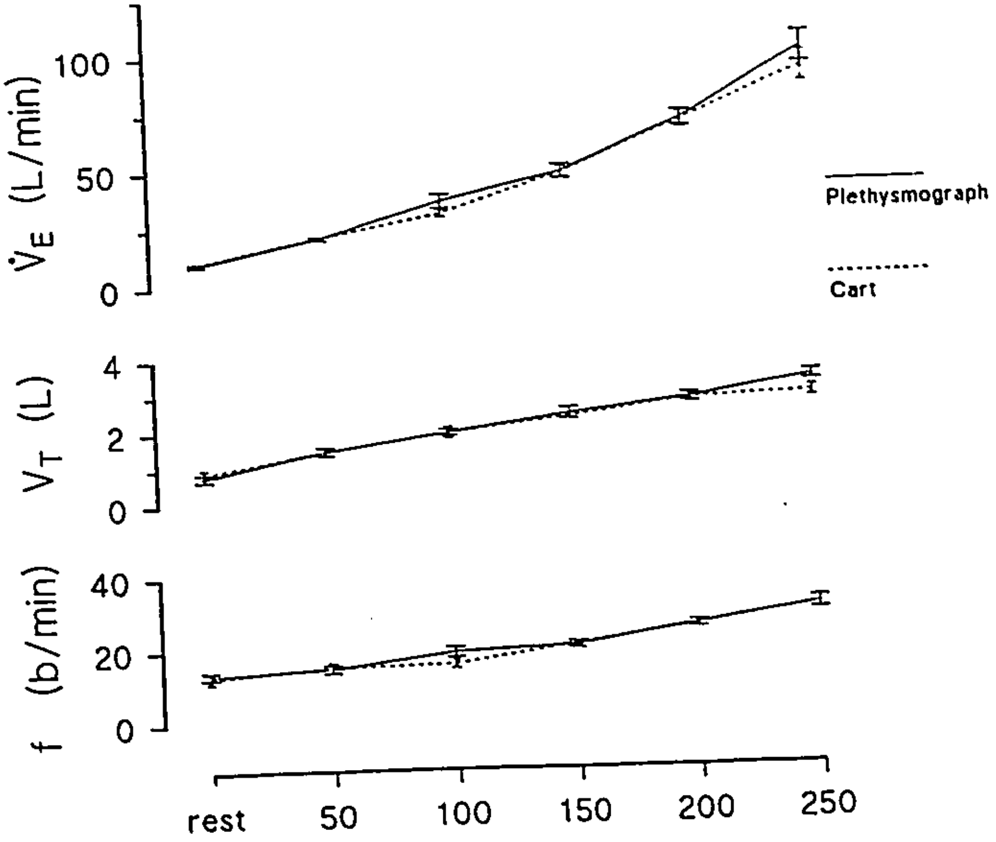
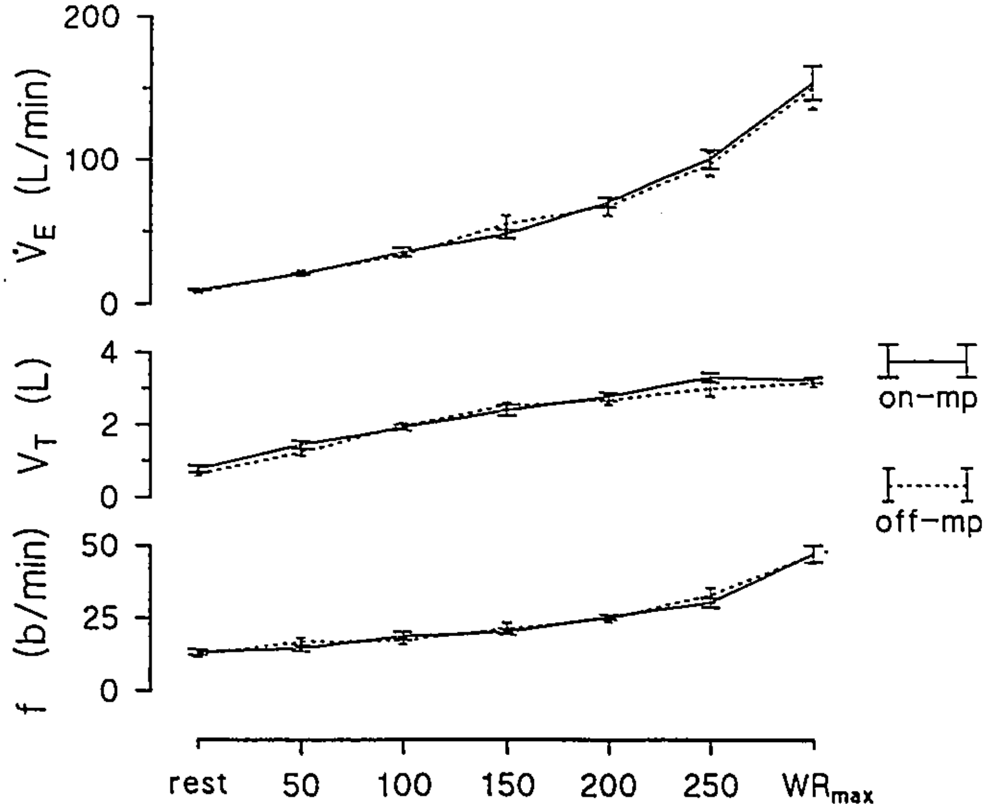


Fig 21 A comparison between measures of $\dot{V}_E$, V_T, and *f*, using direct measures (Cart) and the inductance plethysmograph.



<u>Fig 22</u> A comparison between measures of $\dot{V}_E$, V_T, and *f*, using the inductance plethysmograph under on and off-mp conditions.

MECHANICS OF BREATHING DURING EXERCISE

The between-subject average pressure-volume and flow-volume loops measured under on and off-mouthpiece conditions are presented in fig 23. The loops presented in this figure illustrate the response during each level of progressive exercise as well as during the final collection period of WR_{max}. This figure illustrates the average response of all subjects, individual responses of all subjects are presented in fig 24.

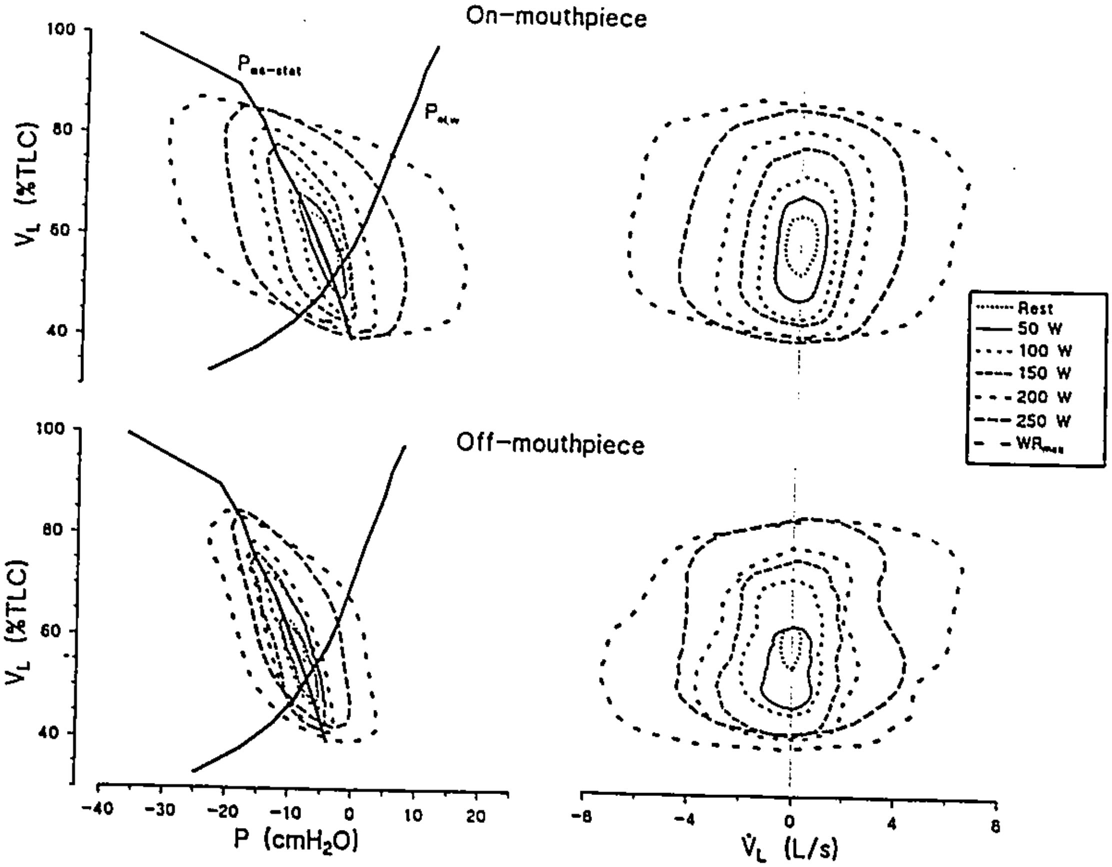


Fig 23 Between-subject average pressure-volume and flow-volume loops recorded at rest and all exercise WR including WR_{max}. On-mp (upper panels) and off-mp (lower panels) measures are included. Pressure-volume are on the left, flow volume on the right.

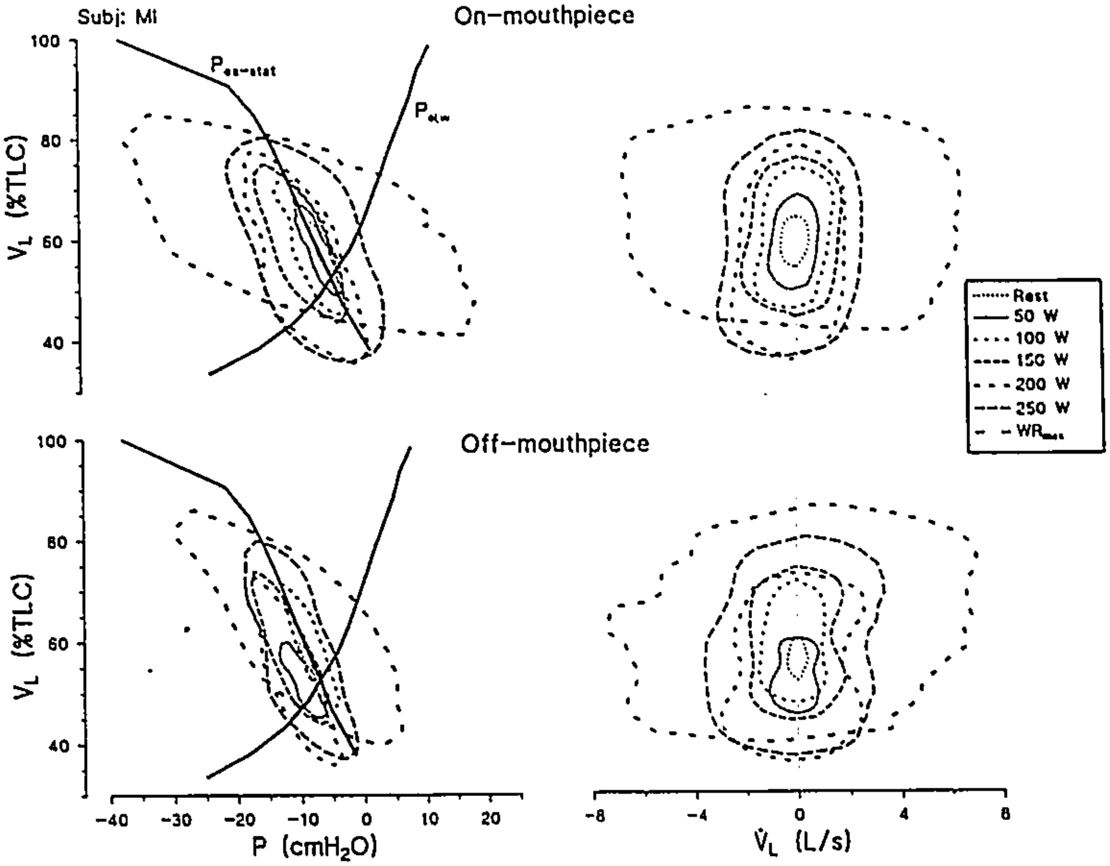


Fig 24 Within-subject average pressure-volume and flow-volume loops recorded at rest and all exercise WR including WR_{max}. Each loop represents the average of three consecutive breaths. Descriptions of each panel are the same as for fig 23. Results for subject MI are found on this page, results of all subjects can be found on following pages.

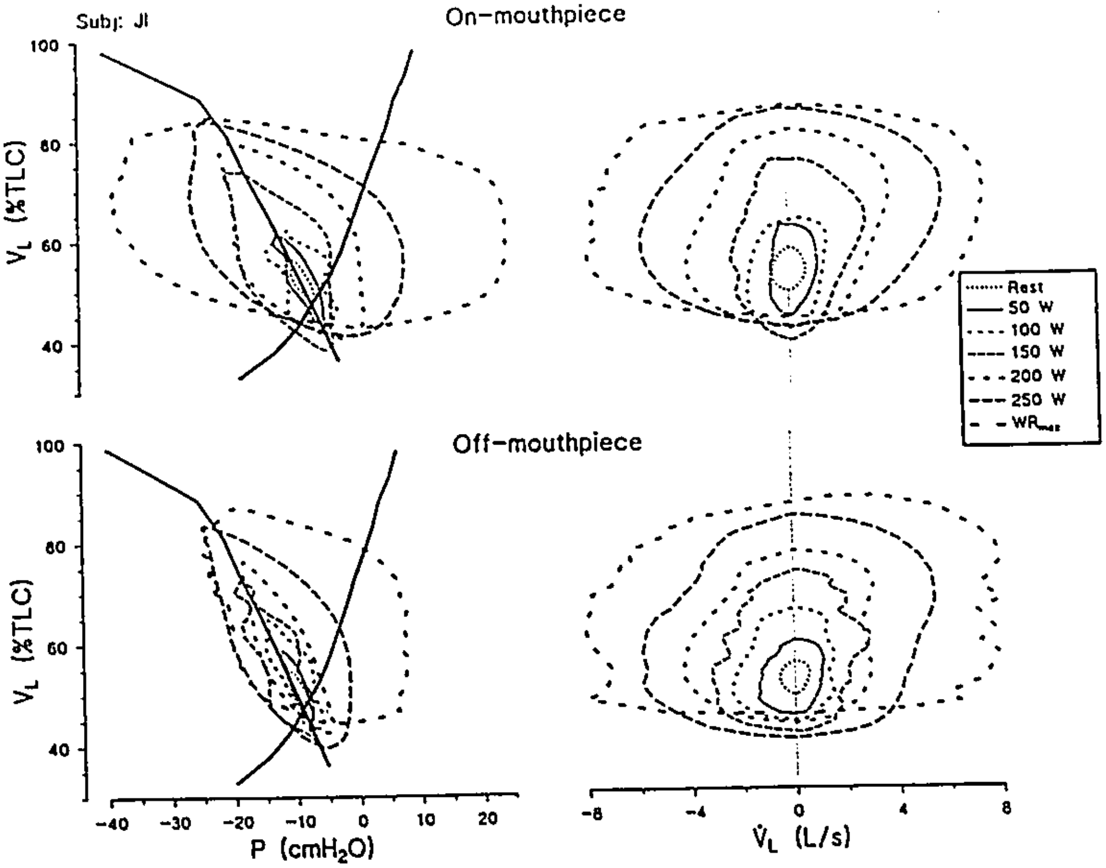

Subj: JI
On-mouthpiece
Off-mouthpiece
100
80
60
40
V_L (%TLC)
-40
-30
-20
-10
0
10
20
P (cmH$_2$O)
-8
-4
0
4
8
$\dot{V}_L$ (L/s)
Rest
50 W
100 W
150 W
200 W
250 W
WR$_{max}$

Fig 24 (Cont'd)

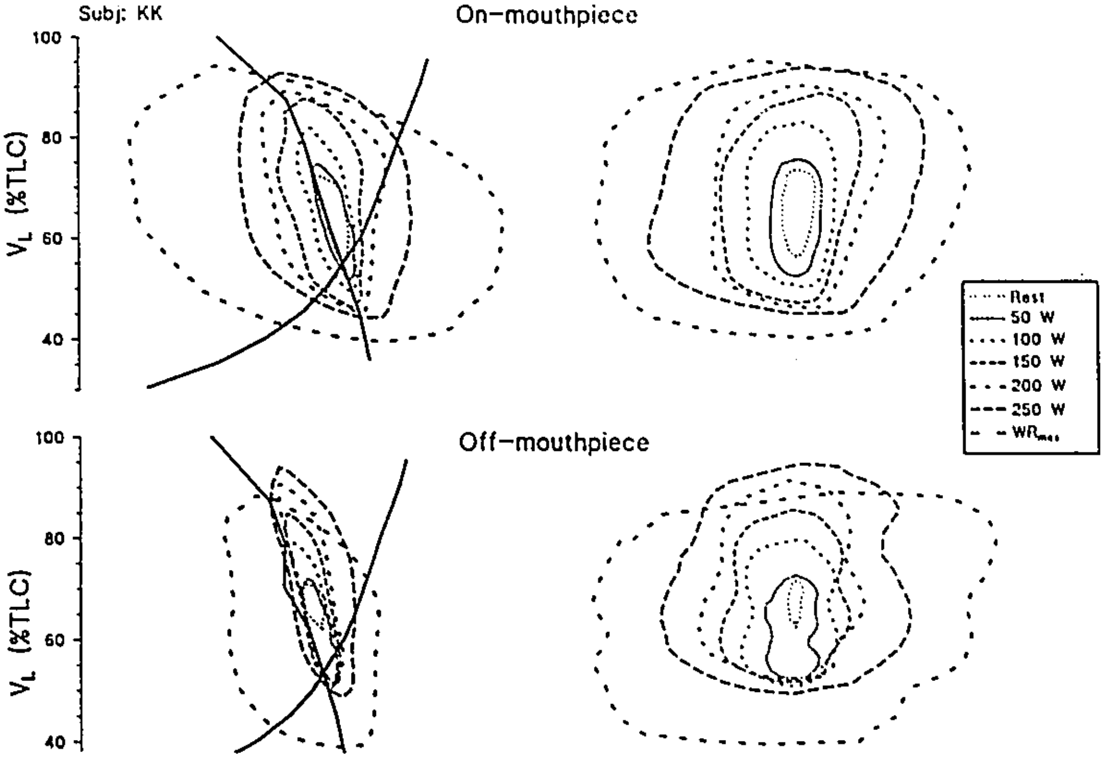

Subj: KK
On−mouthpiece
Off−mouthpiece
V$_L$ (%TLC)
100
80
60
40
V$_L$ (%TLC)
100
80
60
40
Rest
50 W
100 W
150 W
200 W
250 W
WR$_{max}$

Fig 24 (Cont'd)

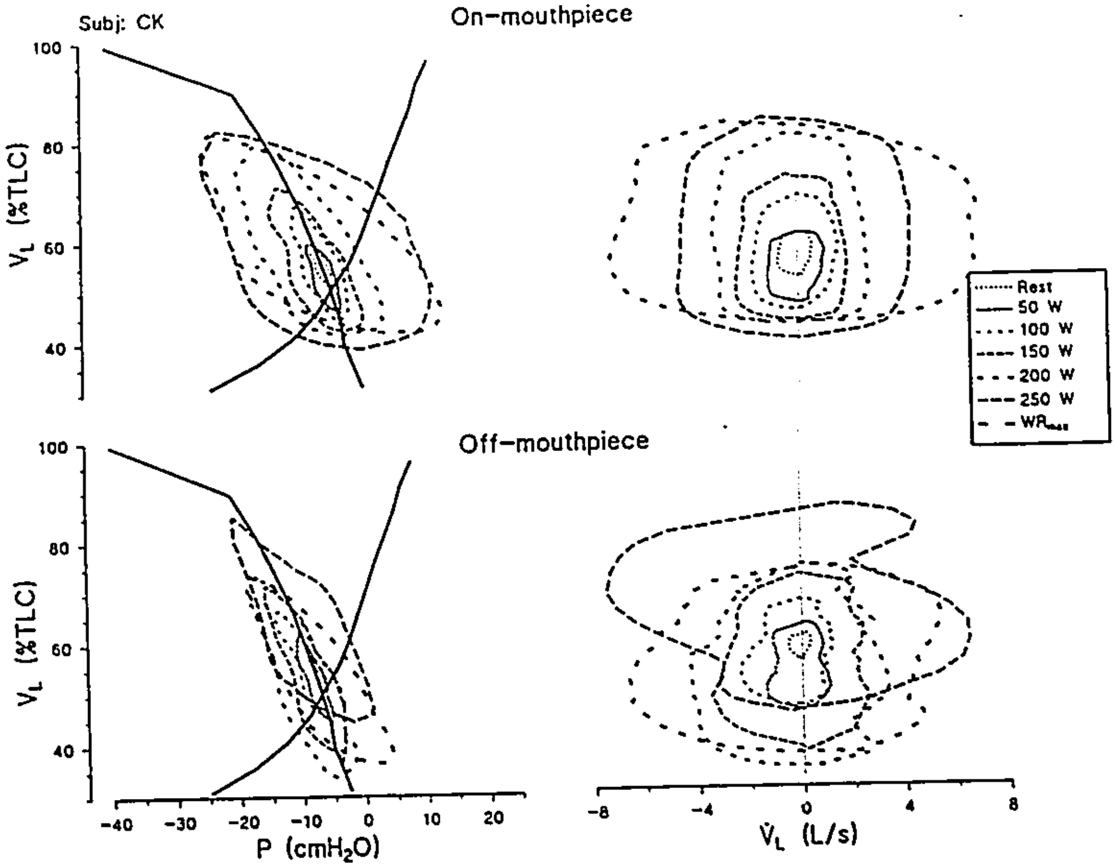

Subj: CK
On–mouthpiece
Off–mouthpiece
V_L (%TLC)
100
80
60
40
V_L (%TLC)
P (cmH$_2$O)
-40
-30
-20
-10
0
10
20
$\dot{V}_L$ (L/s)
-8
-4
0
4
8
Rest
50 W
100 W
150 W
200 W
250 W
WR$_{max}$

Fig 24 (Cont'd)

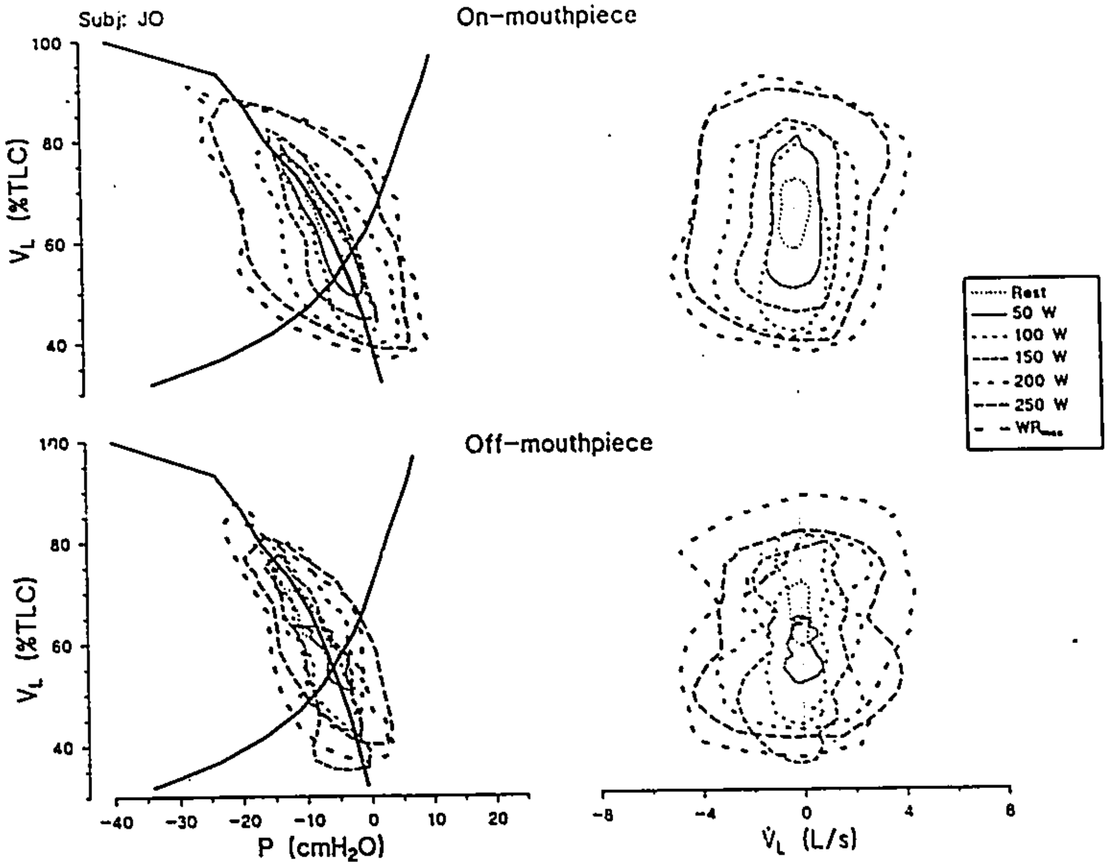

Subj: JO
On–mouthpiece
Off–mouthpiece
100
80
60
40
V_L (%TLC)
-40
-30
-20
-10
0
10
20
P (cmH$_2$O)
-8
-4
0
4
8
$\dot{V}_L$ (L/s)
Rest
50 W
100 W
150 W
200 W
250 W
WR$_{max}$

Fig 24 (Cont'd)

CHANGES IN DYNAMIC COMPLIANCE WITH EXERCISE

Included in the pressure volume diagrams of fig 23 is the average $P_{es\text{-}stat}$ curve, measured under static conditions at rest prior to protocol 1. The shape of this curve is consistent with measures made by Knowles et al. {#26} (see $P_{es\text{-}stat}$ in fig 5). For all WR except WR_{max}, the end-inspiratory (highest) and end-expiratory (lowest) points of the pressure-volume loops fall approximately on the $P_{es\text{-}stat}$ curve. This is also true for the individual results of each subject (fig 24).

At maximal exercise, on-mouthpiece measures of P_{es} made at end-expiration (P_{ee}) and end-inspiration (P_{ei}) do not fall on the $P_{es\text{-}stat}$ curve (fig 23). P_{ei} is more negative than one would expect based on the curve, while P_{ee} is more positive (fig 23). The mean end-expiratory pressure during on-mouthpiece maximal exercise was positive (3.24 ± 2.25 cmh_2O). Observation of each individuals response (fig 24) indicates that this deviation of P_{ei} and P_{ee} away from the $P_{es\text{-}stat}$ curve during maximal exercise did not occur in all subjects.

End-inspiratory measures of P_{es} more negative than the $P_{es\text{-}stat}$ curve have been observed previously in some subjects during maximal exercise (Younes and Kivenen, 1984; Sharratt et al.1987). This change in lung compliance at high breathing frequencies, termed frequency dependence of compliance has been attributed to inequality of time constants (the product of resistance and compliance) in different lung regions (Anthonisen, 1986). With a short inspiratory time, regions with long time constants (ie. high resistance and/or compliance) fail to reach the volume expected for the end-inspiratory pressure achieved. As a result, there is an apparent decrease in the lung compliance (ie. smaller lung volume for a given P_{pl} under static conditions), which would account for the observation of end-inspiratory esophageal pressures more negative than static measures made at the same volume ($P_{es\text{-}stat}$)

End-expiratory esophageal pressure greater than $P_{es\text{-}stat}$ has been observed in some subjects at maximal exercise (Olafsson and Hyatt, 1969; Sharratt et al.1987; Henke et al.1988). Although this phenomenon has never been formally addressed, during personal discussion regarding his observations (Henke et al.1988; Sharratt et al.1987), Dempsey suggested that the positive end-expiratory pressures probably occur due to airway closure at the low end-expiratory lung volumes observed during exercise.

A gradient of pleural pressures exists in the lung; Milic-Emili has estimated that this gradient is from -8.5 cmh_2O at the apex, to -2.5 cmH_2O at the base in upright humans at FRC (Milic-Emili et al.1966). Positive measures of P_{pl} have been obtained near the base of dog lungs at static volumes below FRC (Hoppin et al.1969) (the pressure gradient in these dogs at FRC was from -7.5 to -2.2 cmH_2O). It thus appears possible that at maximal exercise, positive end-expiratory P_{es} in some subjects occurred as a result of balloon placement near the base of the lung and the low end-expiratory lung volume achieved with exercise. End-expiratory lung volume during 200W and 250W exercise was as low as at WR_{max}, but at these WR, end-expiratory esophageal pressure measures fell directly on the $P_{es\text{-}stat}$ curve (see fig 23). This might be explained by the suggestion of Rodarte et al. (1975) that during expiration, the volume at which the airways close (closing volume), and thus, the volume at which P_{pl} might become positive, may be influenced by the expiratory flow rate. They proposed that airway closure may occur in lower airways, at the point of flow limitation (ie when $P_{pl} = P_{maxeff}$) and should therefore occur at progressively higher lung volumes as flow rate increases (Rodarte et al.1975).

An alternative hypothesis is that the mechanism responsible for end-expiratory pressures greater than $P_{es\text{-}stat}$ is the same as that for end-inspiratory pressures less than $P_{es\text{-}stat}$. If expiratory time were short enough, flow from regions with long time constants to regions with short time constants might still be taking place at end-expiration. This might account for the positive end-expiratory P_{es} without necessarily indicating airway closure.

VARIABILITY IN MEASUREMENT OF OFF-MOUTHPIECE LUNG VOLUME

The end-inspiratory and end-expiratory points of several subjects' off-mp pressure-volume loops do not fall on the $P_{es\text{-}stat}$ curve (fig 24). In some cases these points are as much as 15 %TLC away from the curve. Error in the V_L measurement under off-mouthpiece conditions, owing to the inability of inductance plethysmography to follow absolute lung volume over a prolonged period of time during exercise is the most likely explanation (Sharratt et al.1987).

Sackner et al. (1980) have observed that minor postural adjustments will result in changes in the relationship between the plethysmograph signal and the volume changes of the abdominal and rib cage compartments. These findings likely reflect a third degree of freedom in the motion of the chest wall. Postural changes, such as extension or flexion of the spine may produce changes in lung volume without necessarily changing the diameter of either rib cage or abdominal compartment.

It is likely that slight movement by the subject during the time between off-mp collection and the calibration (approximately 40s), and during insertion of the mouthpiece was enough to produce changes in the gain and/or offset of the plethysmograph signal and therefore, errors in off-mp V_L measures. This possibility was investigated by re-plotting the on-mp pressure-volume loops recorded during protocol 1 for subject CK (fig 25). Rather than using the correct regression equation to calibrate the plethysmograph signal for this plot, the one from the previous WR was used. Any change in the gain and/or offset of the plethysmograph signal owing to subject movement between collection periods should be reflected by a volume shift of these pressure- volume loops. Fig 25 shows that using the previous WR calibration resulted in some cases in large volume errors in the placement of the pressure-volume loops. It appears that despite the care taken to prevent subject movement between off and on-mp measures, enough movement occurred to produce errors in off-mp V_L measures. This observation illustrates the importance of calibrating the plethysmograph signal immediately after data collection.

Interestingly, following between-subject averaging, off-mouthpiece P_{ei} and P_{ee} fall approximately on the $P_{es\text{-}stat}$ curve (fig 23). This observation suggests that the errors in off-mp V_L measurement were random in nature, and that the between-subject averaging resulted in cancelling of errors. All further analysis of off-mp respiratory mechanics are based on this assumption, that errors in V_L measurement have been cancelled by between-subject averaging.

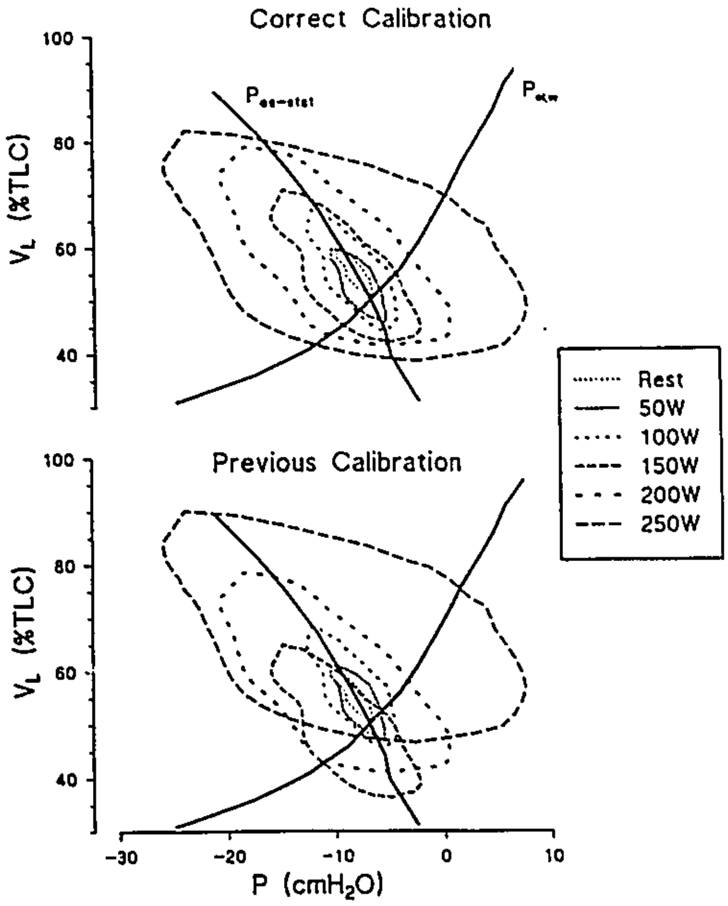
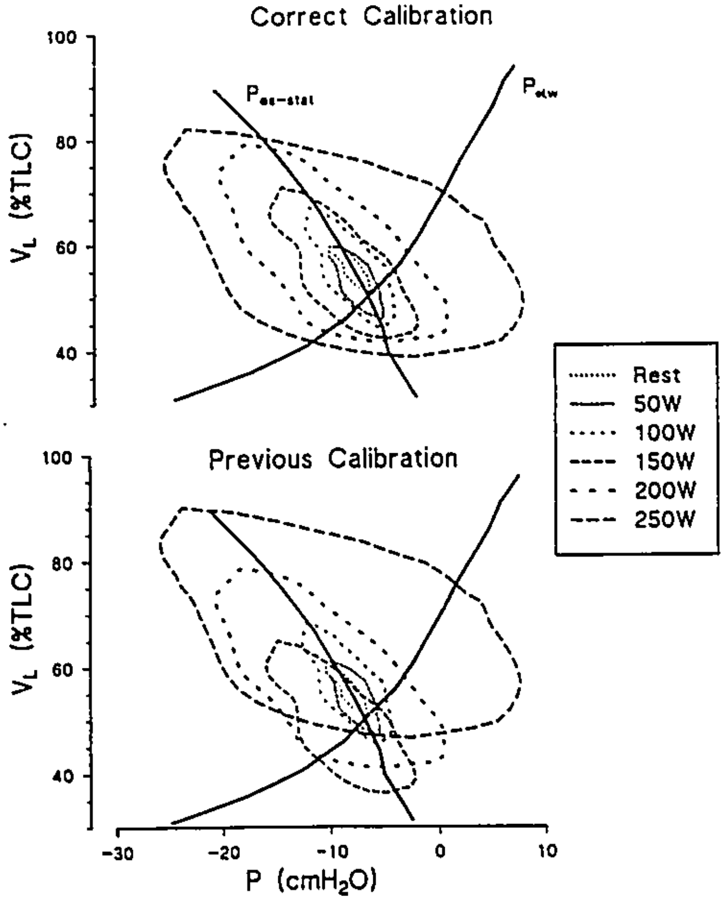


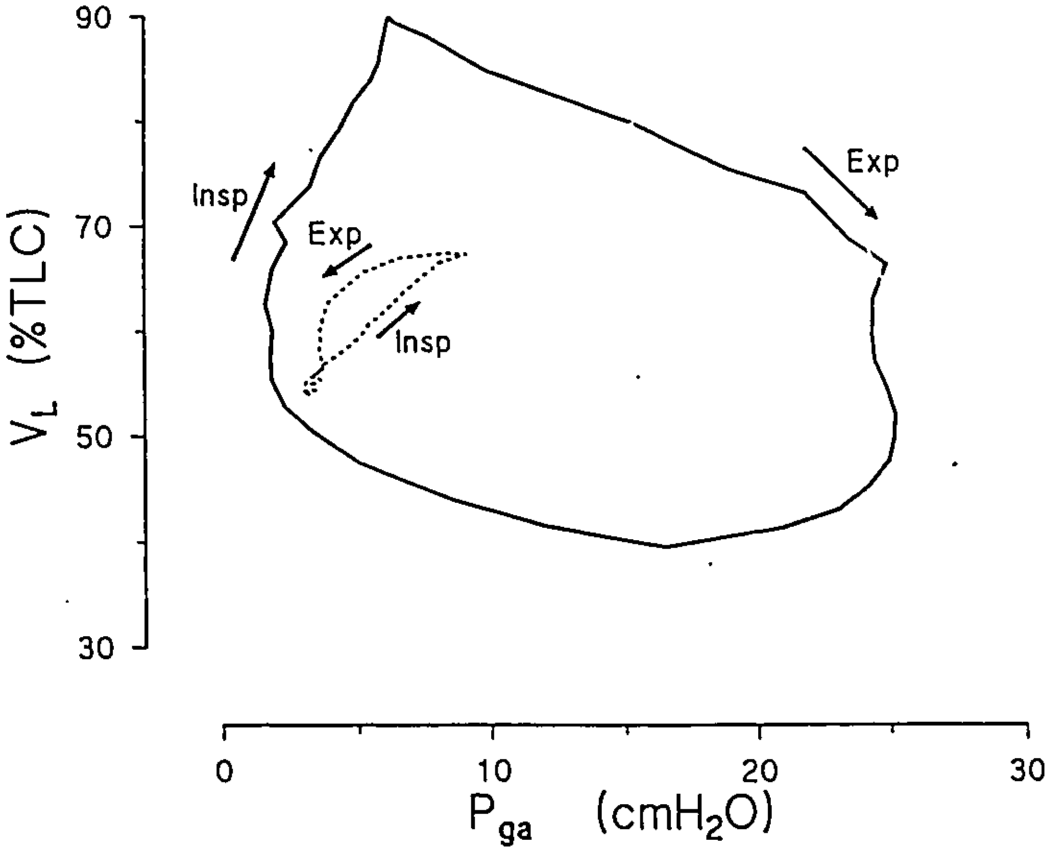
Fig 25 Illustration of the importance of calibrating plethysmograph immediately following data collection. Top panel is on-mp pressure volume loops from subject CK. Bottom panel is same loops, but with V_L calculated using calibration factor from the previous collection period.

Correct Calibration
Previous Calibration
$P_{es-stat}$
P_{stw}
V_L (%TLC)
100
80
60
40
P (cmH_2O)
-30
-20
-10
0
10
Rest
50W
100W
150W
200W
250W

GASTRIC PRESSURE RESPONSE

Owing to a leak in the balloon circuit, gastric pressures were measured during maximal exercise for three subjects only. Gastric pressure-lung volume loops for these subjects at rest and maximal exercise are presented in fig 26.
These responses are similar to previous measures made during maximal exercise by Grimby et al. (1976) and Henke et al. (1988).

Grimby et al. (1976) suggest that the muscle activity responsible for the motion of the chest wall may be inferred from the direction of the pressure-volume loop. At rest, the P_{ga}-V_L loop is counter clockwise; P_{ga} is greatest during inspiration, as the contracting diaphragm displaces the abdominal wall and its content. During maximal exercise the loop is clockwise; P_{ga} is greatest during expiration, indicating abdominal muscle activity is responsible for some chest wall motion during expiration.



<u>Fig 26</u> Gastric pressure-lung volume responses. Average responses of three subjects at rest (dashed line) and at WR_{max} (solid line). Inspiratory and expiratory directions are indicated.

CHANGES IN EELV WITH EXERCISE

End-expiratory lung volume is illustrated in fig 23 as the lowest point in each of the pressure-volume loops. EELV decreased as work rate increased, the mean values are presented in table 5.

Table 5 Mean EELV (%TLC) at rest and during exercise.

	Rest	50W	100W	150W	200W	250W	max
On-mp	53.00 (±3.7)	47.57 (±3.6)	43.99 (±3.8)	42.91 (±3.0)	40.39 (±3.7)	39.65 (±3.1)	40.27 (±2.5)
Off-mp	54.90 (±5.3)	47.33 (±3.6)	45.90 (±3.1)	41.38 (±6.4)	41.24 (±7.0)	42.14 (±4.6)	39.27 (±3.3)

Because of the larger variability in off-mp measures, the EELV results were analyzed using a one way ANOVA$_{rm}$ of on-mp data, and a two way ANOVA$_{rm}$ of on and off-mp data. The two way ANOVA$_{rm}$ did not show a significant difference between EELV under on-mp and off-mp conditions ($p>0.05$) but did show a significant influence of WR on EELV ($p < 0.05$). The one way ANOVA$_{rm}$ of on-mp data also showed this significant effect of WR on EELV. Post hoc testing of the on-mp data showed a significant decrease in EELV between rest and 50W exercise ($p < 0.05$) and a further significant decrease between 50W and 100W exercise ($p < 0.05$). There were no further significant changes in EELV as WR was increased above 100W ($p > 0.05$).

Discussion

EELV decreased by approximately 14 %TLC between rest and maximal exercise. This is in agreement with nine previous studies in which EELV was measured during intense or maximal exercise (Asmussen and Christensen, 1939; Grimby et al.1968; Mead and Agostoni, 1964; Kagawa and Kerr, 1970; Linnarsson, 1974; Lind and Hesser, 1984; Sharratt et al.1987; Henke et al.1988; Johnson et al.1990). The average fall in EELV observed in these studies was approximately 10 %TLC (ranging from 4% (Kagawa and Kerr, 1970) to 15% (Asmussen and Christensen, 1939)).

Several studies have shown no change in EELV with exercise (Hanson et al.1962; Chiang et al.1965; Bouhuys et al.1956; Stubbing et al.1980). Three of those studies involved mild exercise levels where EELV fell by approximately 3 %TLC but failed to reach significance (Hanson et al.1962; Chiang et al.1965; Bouhuys et al.1956). The study by Stubbing et al. (1980) involved moderate exercise (130W) but failed to show any decrease in EELV. The posture of subjects in that study may have influenced the findings; subjects were in a body box and were required to cycle with their legs raised perpendicular to their trunk.

Two studies have shown a fall in EELV of approximately 5 %TLC during mild exercise with a subsequent return to resting levels with more intense exercise (Kiers et al.1980; Younes and Kivenen, 1984). In the current study, EELV measures increased (i.e. returned towards resting values) between 250W and WR_{max} in three subjects (MI by 4.4 %TLC, JI by 3.4 %TLC, CK by 3.2 %TLC). The nature of the maximal flow-volume relationship may make it necessary for some subjects to increase end-expiratory lung volume at very high levels of ventilation. Maximal inspiratory and expiratory flow at a given lung volume are illustrated in fig 27. The dashed loop in fig 27 illustrates a pattern of breathing where expiratory flow is limited by the maximum achievable flow. Thus, without changing operating lung volume, $\dot{V}_E$ could only be increased by increasing inspiratory flow. The dotted line illustrates a pattern of breathing with increased EELV, thus eliminating the portion where expiratory flow is limited. The result of this change in breathing pattern would be increased $\dot{V}_E$ without requiring increased inspiratory flow. This method of increasing $\dot{V}_E$ may be important at very high levels of ventilation, for example the levels reached by elite athletes during exercise.

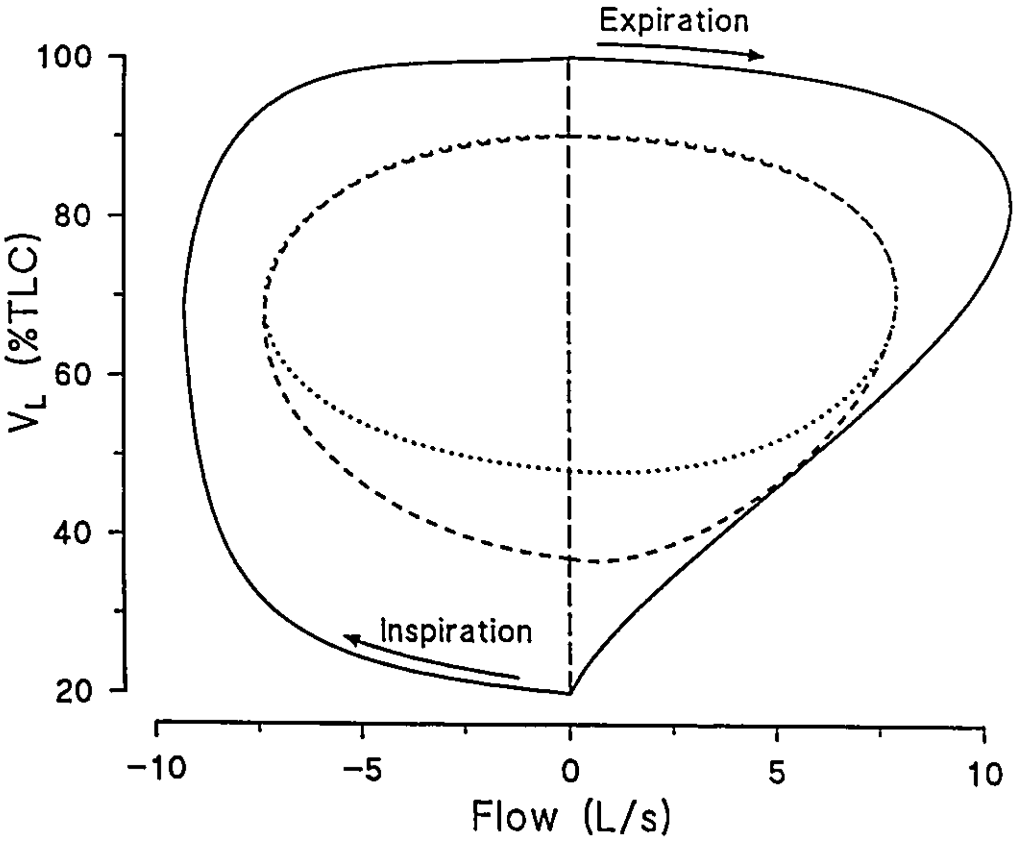


Fig 27 Potential benefit from raising EELV at very high levels of ventilation. Solid curve is maximum achievable inspiratory and expiratory flow. Dashed curve represents breathing pattern with operating lung volume at levels typically seen during exercise. Dotted loop represents breathing pattern with raised EELV.

There are two benefits of breathing with an end-expiratory volume less than FRC. First, at lower lung volumes the inspiratory muscles would be longer and thus able to develop greater force during inspiration (Agostoni and Fenn, 1960). Secondly, the elastic energy stored during compression of the chest wall could be recovered during inspiration, thus reducing the work required of inspiratory muscle.

Measures made during increased ventilation by Grassino et al. (1981) indicate that a component of the pressure required for inspiration is achieved through recoil of elastic structures. In that study, hypercapnia was used to increase ventilation while mouth and gastric pressure were measured 0.1s after the beginning of inspiration ($P_{0.1}$). The authors argued that if inspiration occurred as a result of diaphragm contraction, then the abdominal $P_{0.1}$ would be more positive than the mouth $P_{0.1}$. While this was true for some subjects, in others the abdominal and mouth $P_{0.1}$ were essentially the same, suggesting that much of the inspiratory pressure 0.1s after the onset of inspiration was achieved due to the recoil of the abdominal contents.

The contribution from recoil of abdominal contents to the pressure required for inspiration is also suggested by the gastric pressure-lung volume loops in fig 26. P_{ga} is less during inspiration at maximal exercise than it had been at the same lung volume at rest. The additional negative P_{ga} during inspiration at maximal exercise would be transmitted across the diaphragm, thus contributing to the required pleural pressure. It seems likely that the source of this pressure difference during inspiration is abdominal recoil, following abdominal compression by muscle activity during expiration.

Other explanations for inspiratory P_{ga} being lower at maximal exercise than at rest are less attractive. P_{ga} would be reduced if the rib cage contribution to the negative pleural pressure during inspiration exceeded that of the diaphragm. However, for this to be the only explanation of the lower P_{ga}, the diaphragm would have to be ascending during inspiration rather than descending.

Another explanation for the lower P_{ga} during WR_{max} is that abdominal muscle activity may have been greater during inspiration at rest than during exercise. Recordings of abdominal EMG activity at rest and during increased ventilation either due to hypercapnia (Campbell and Green, 1955), or exercise (Naus, 1989) make this an improbable explanation. In both cases, the abdominal muscles were inactive at rest, but active to some extent in early inspiration during exercise or hypercapnia.

End-expiratory lung volume was not significantly different between on ard off-mp conditions (table 5). While no previous comparisons have been made between on and off-mp EELV measurement, Henke et al. (1988) observed no significant difference between on and off-mp measures of end-expiratory P_{es} during exercise to near maximal levels. These findings support the current observation that the decrease in EELV during exercise occurs whether the subject is breathing freely or through a mouthpiece.

CHANGES IN EXPIRATORY FLOW AND ESOPHAGEAL PRESSURE WITH EXERCISE

Expiratory P_{es} and $\dot{V}_{exp}$ increased at a given lung volume as exercise WR increased (fig 23). The mean values for expiratory P_{es} and $\dot{V}_{exp}$, measured at 50, 60, and 70 %TLC during exercise are illustrated in fig 28. At some work rates some subjects did not achieve one or more of the V_L included on fig 28. When this occurred, if possible the value from the between-subject average response was used (these points do not have error bars). Significant increases in $\dot{V}_{exp}$ occurred with each increase in WR at each lung volume ($p<0.05$). Significant increases in P_{es} occurred with each increase in WR at 50 and 70 %TLC and with each increase in WR above 150W at 60 %TLC ($p<0.05$).

Each curve in fig 28 changes from dashed to solid at the point where P_{es} is greater than $P_{el,w}$ at that lung volume. Increases in $\dot{V}_{exp}$ above this point are attributed to expiratory muscle pressure. All values of P_{es} at 50 %TLC were greater than $P_{el,w}$.

Analysis of this type was not possible for off-mp data, because of the higher variability in V_L measurement. The between-subject responses in fig 23 show that $\dot{V}_{exp}$ and P_{es}

increased under off-mp conditions in a similar manner to on-mp conditions.

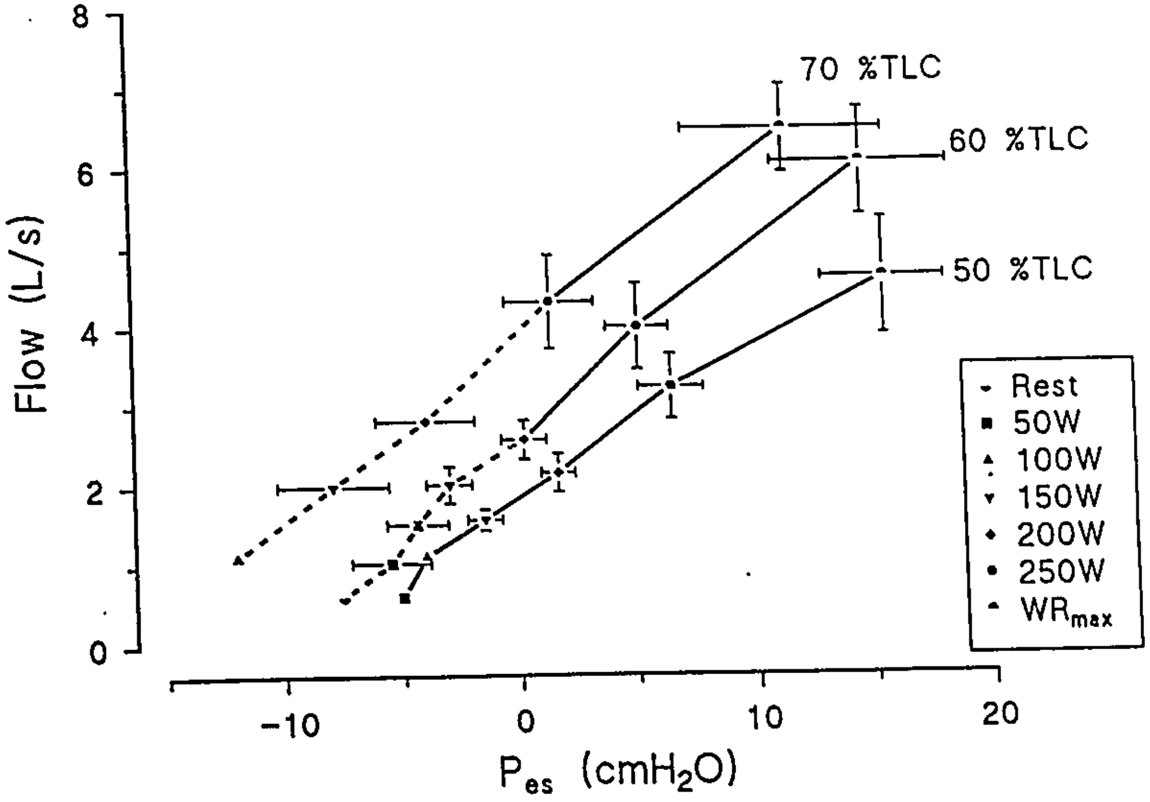


Fig 28 Illustration of the increases in P_{es} and expiratory flow occurring with increases in exercise WR. Increases in P_{es} were associated with increased flow at all three lung volumes. The point where each curve switches from dashed to solid indicates where $P_{el,w}$ was exceeded.

Discussion

Expiratory flow increased at a given V_L as WR increased. This increase in flow was achieved for the most part through increases in pleural pressure during expiration, indicated by the significant increases in P_{es}.

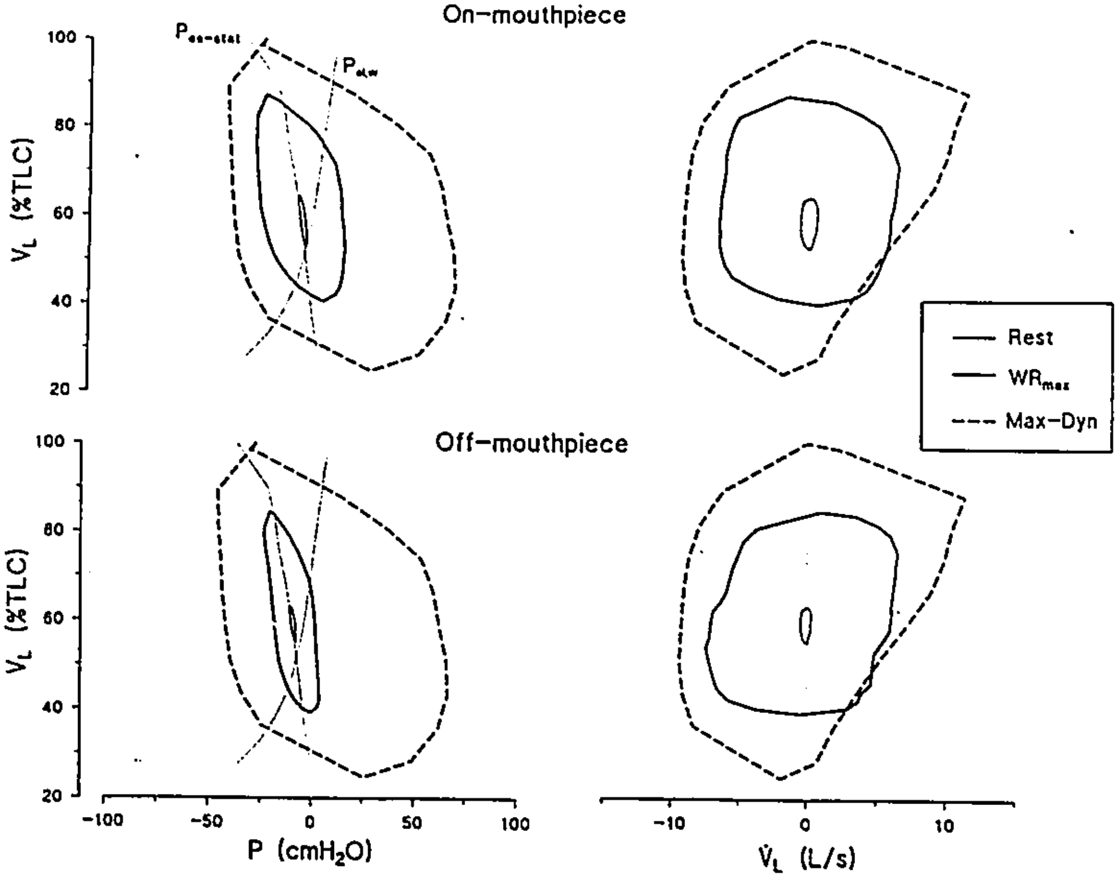
The portion of expiratory flow attributable to expiratory muscle activity is indicated on each curve in fig 28 as that part above the transition from dashed to solid lines (i.e. the portion where P_{es} is greater than $P_{el,w}$). Hence, at WR_{max} during expiration, at 70 %TLC one third of the 6 L/s is attributed to expiratory muscle activity. Similarly, at 60 %TLC one half of the expiratory flow is attributed to expiratory muscle activity, while at 50 %TLC all expiratory flow is attributed to expiratory muscle activity.

P_{es} greater than $P_{el,w}$ has been shown during exercise in previous investigations (Margaria et al.1960; Grimby et al.1976; Younes and Kivenen, 1984). Whether expiratory activity contributed to increased $\dot{V}_{exp}$ was not addressed in any of these studies. The results of the present study show that expiratory muscle activity accounts for a large portion of expiratory flow during exercise.

EFFECTIVENESS OF EXPIRATION DURING EXERCISE

If expiratory pressure became ineffective (i.e. greater than P_{maxeff}) during exercise, a point would be reached where further increase in pressure would not result in increased flow. In fig 28, at all three lung volumes, for each increase in P_{es} there is a concomitant increase in flow, indicating that ineffective expiratory activity did not occur in the range from 50 to 70 %TLC.

Expiratory effectiveness was further investigated by comparing flow during maximal exercise with the maximum achievable flow. Between-subject average pressure-volume and flow-volume loops measured on and off-mp during maximal exercise are illustrated in fig 29. Included in fig 29 are the pressure-volume and flow-volume loops illustrating the maximal dynamic effort. Within-subject average results for all subjects are illustrated in fig 30. Pleural pressure remained effective for the majority of expiration at WR_{max} since $\dot{V}_{exp}$ remained less than that developed during the max-dyn effort. However, between 55 and 40 %TLC, flow developed during exercise reached or exceeded that developed during the max-dyn effort. P_{maxeff} may have been exceeded at this range of V_L.



<u>Fig 29</u> Between-subject pressure and flow-volume loops recorded at rest, WR_{max} and during maximal dynamic (Max-Dyn) efforts. Max-dyn recordings were recorded immediately upon cessation of WR_{max} exercise while the subject breathed to and from the spirometer.

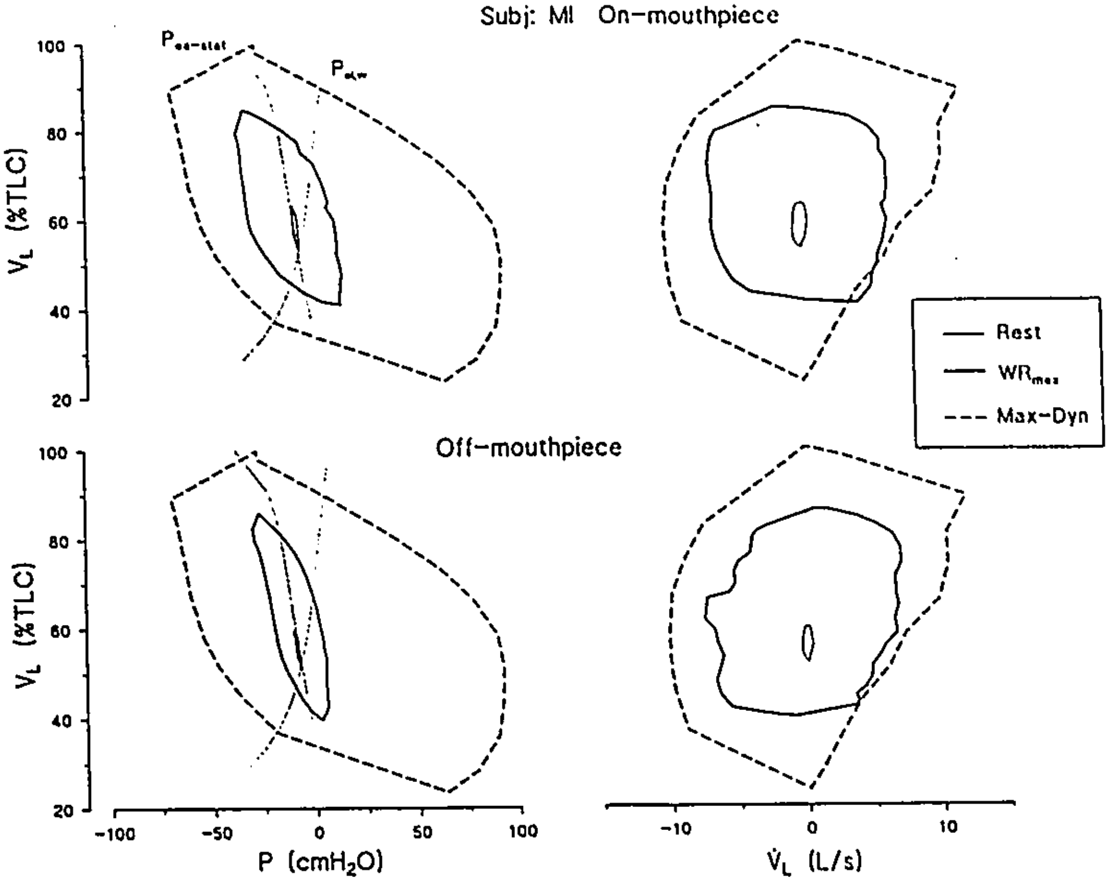
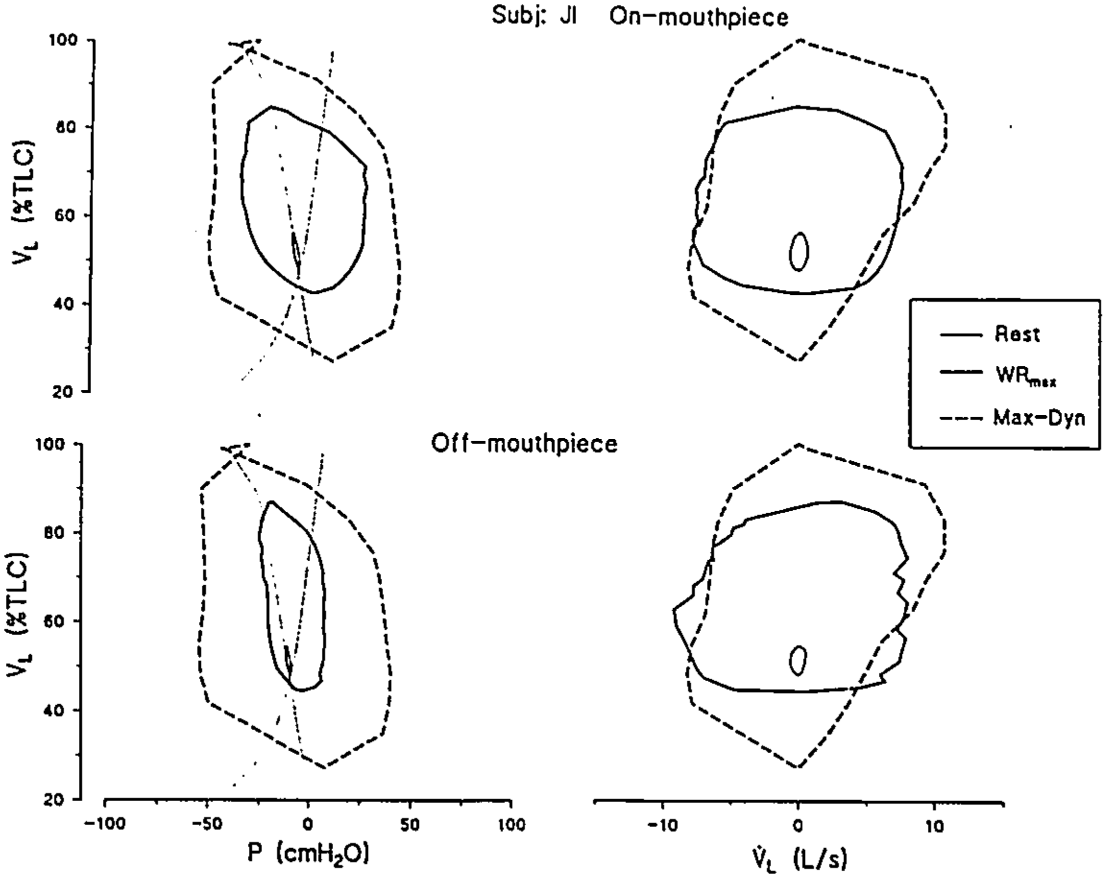
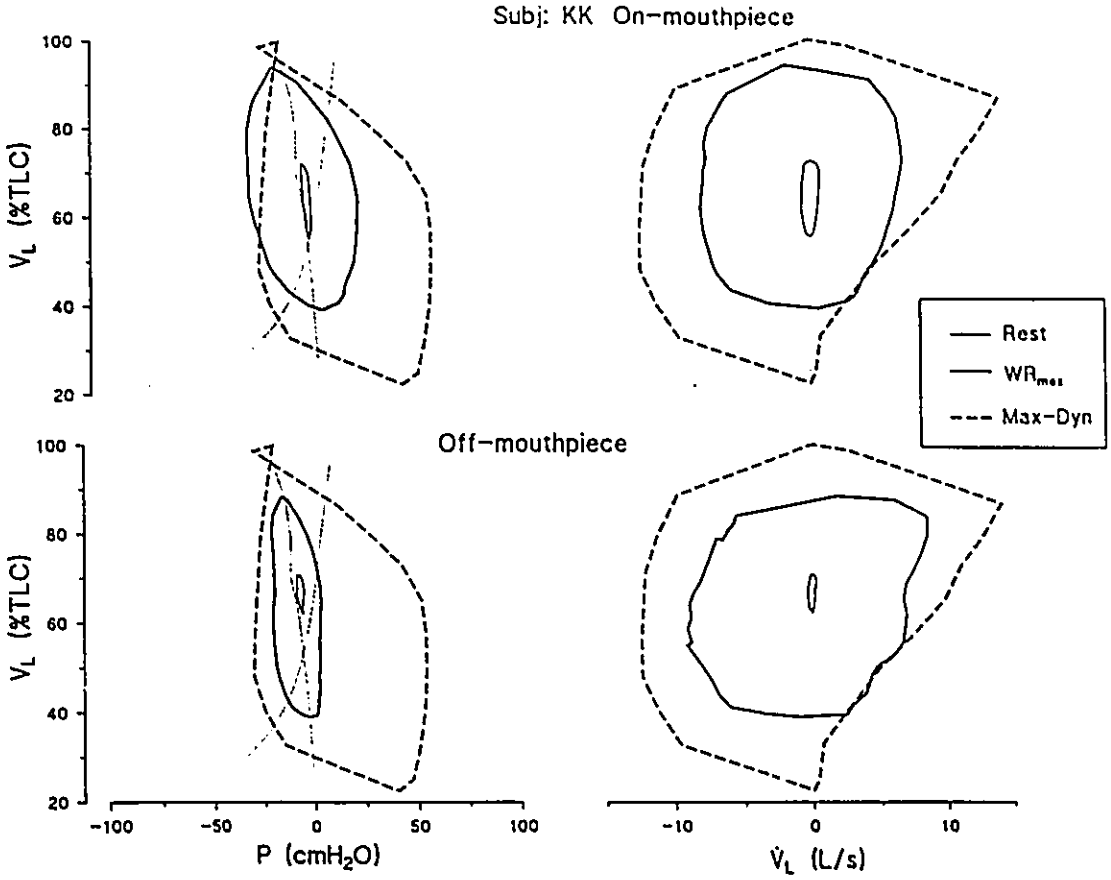


Fig 30 Within-subject pressure and flow-volume loops recorded at rest, WR_{max} and during maximal dynamic (Max-Dyn) efforts. The results for subject MI are on this page. All other subjects' results can be found on following pages.


Subj: JI On-mouthpiece
Off-mouthpiece
V_L (%TLC)
100
80
60
40
20
-100
-50
0
50
100
P (cmH_2O)
-10
0
10
$\dot{V}_L$ (L/s)
Rest
WR_{max}
Max-Dyn

<u>Fig 30</u> (Cont'd)


Subj: KK On-mouthpiece
Off-mouthpiece
100
80
60
40
20
V_L (%TLC)
-100
-50
0
50
100
P (cmH$_2$O)
-10
0
10
$\dot{V}_L$ (L/s)
Rest
WR$_{max}$
Max-Dyn

<u>Fig 30</u> (Cont'd)

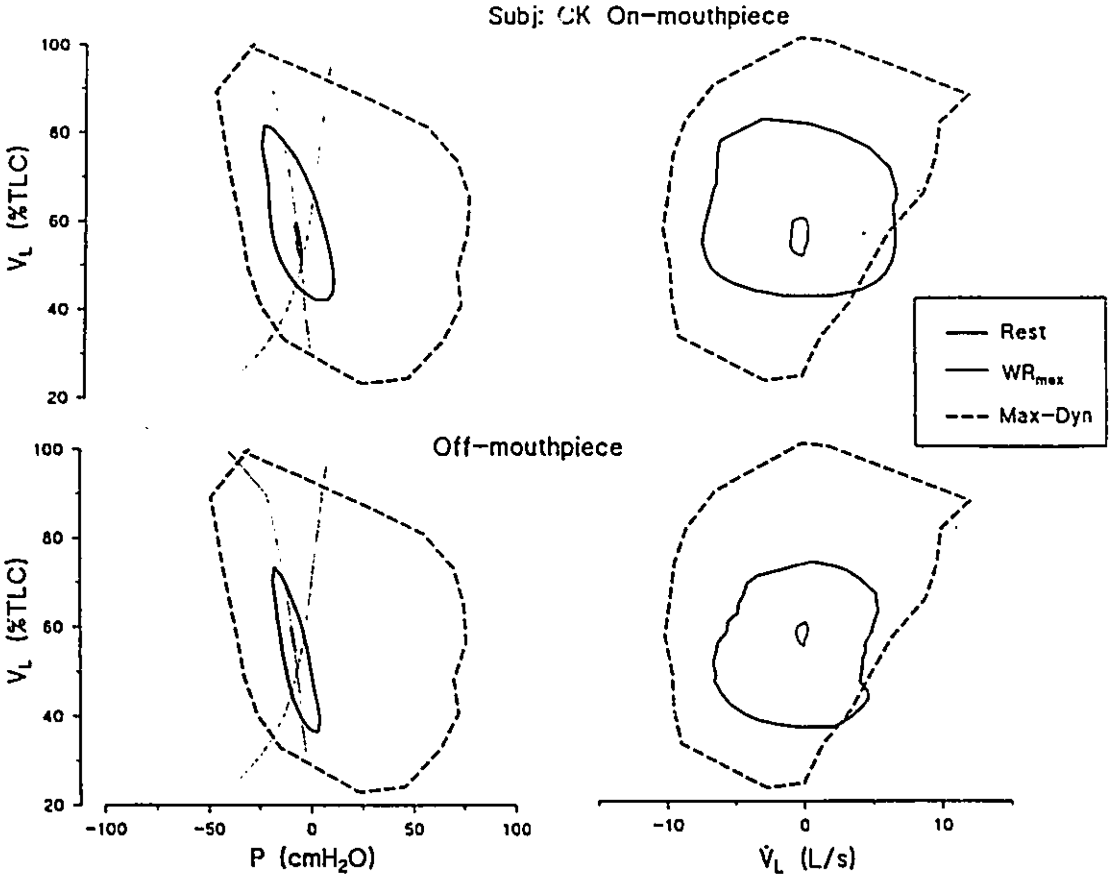

Subj: CK On-mouthpiece
Off-mouthpiece
V_L (%TLC)
100
80
60
40
20
P (cmH$_2$O)
-100
-50
0
50
100
$\dot{V}_L$ (L/s)
-10
0
10
Rest
WR$_{max}$
Max-Dyn

Fig 30 (Cont'd)

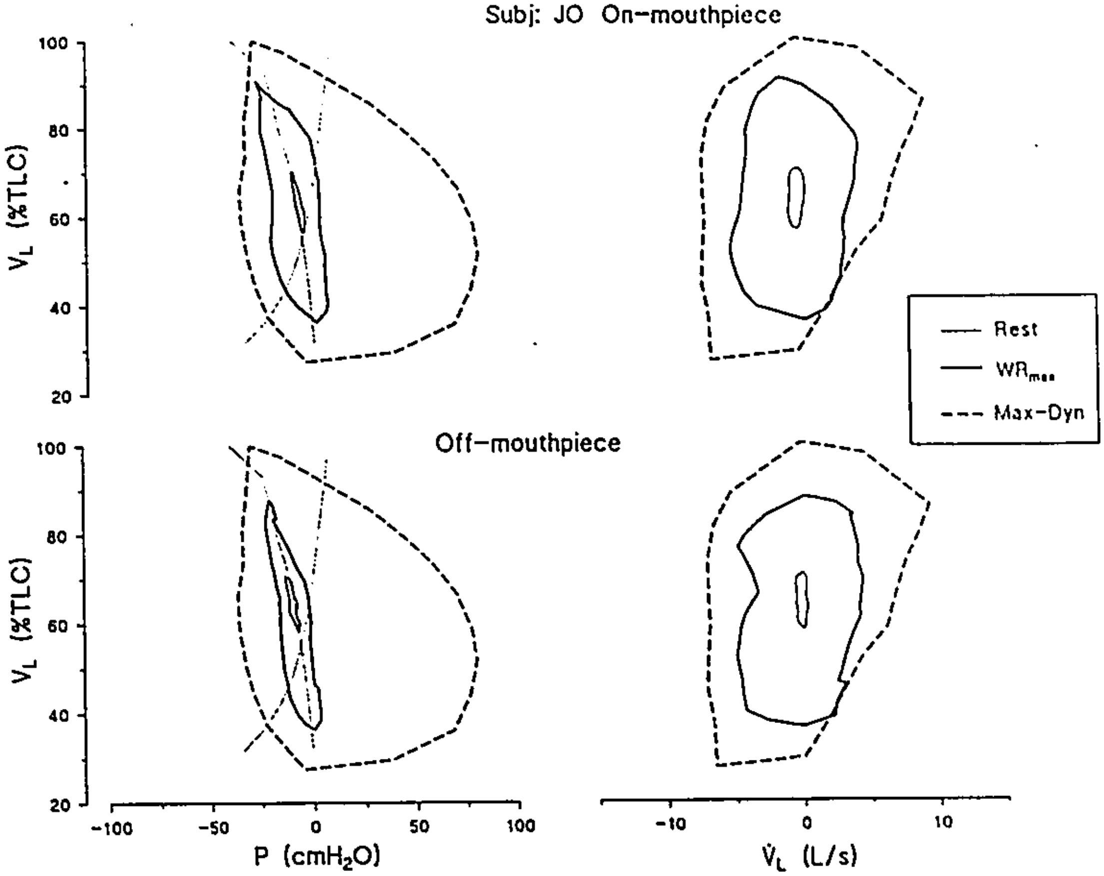
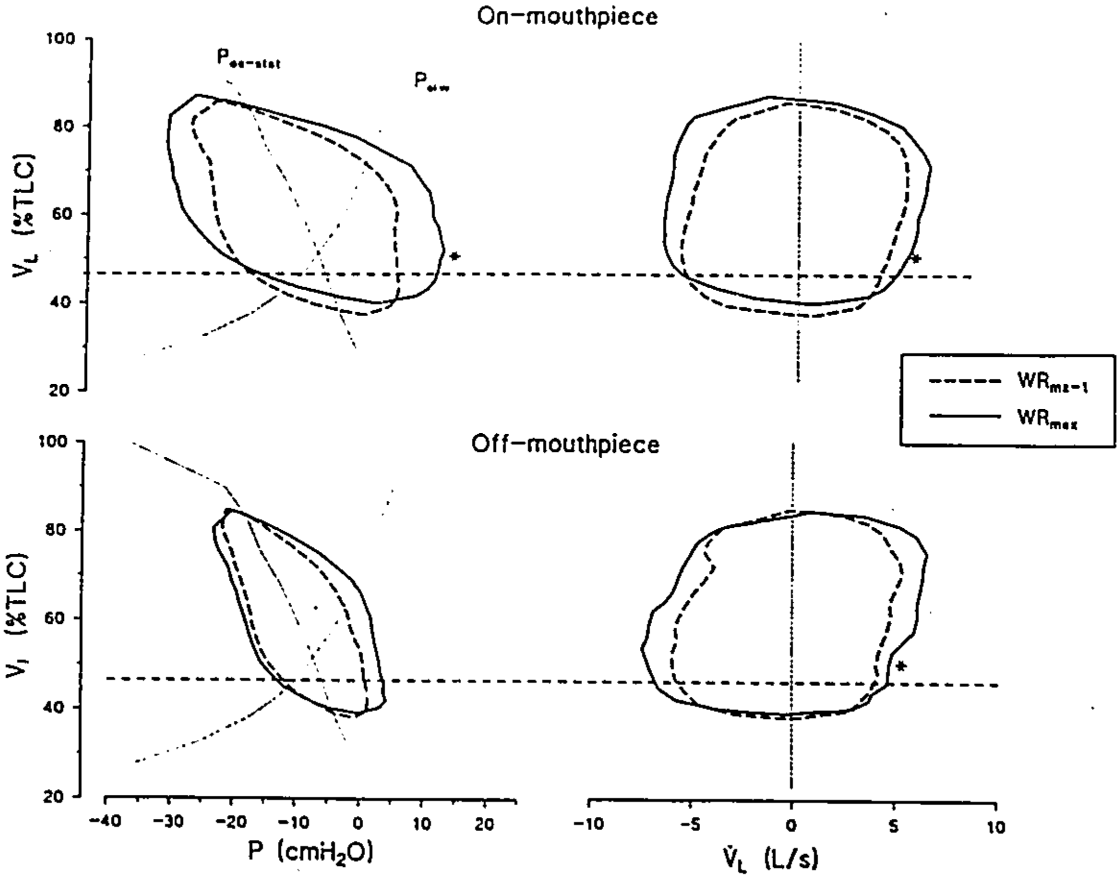

Subj: JO On-mouthpiece
Off-mouthpiece
V_L (%TLC)
100
80
60
40
20
-100
-50
0
50
100
P (cmH$_2$O)
-10
0
10
$\dot{V}_L$ (L/s)
Rest
WR$_{max}$
Max-Dyn

Fig 30 (Cont'd)

To investigate the extent to which P_{maxeff} may have been exceeded during the final collection period of maximal exercise, the pressure-volume and flow-volume loops measured earlier during that protocol were examined. Pressure-volume and flow-volume loops measured in the final collection period of maximal exercise (WR_{max}) are compared to measures made approximately 1 minute (76 ± 13s) earlier (WR_{mx-1}) in fig 31. Ventilation at the earlier stage of maximal exercise was significantly less (121 ± 8 vs 153 ± 12 L/min;$p< 0.05$). P_{es} and $\dot{V}_{exp}$ were measured during expiration at a lung volume of 47 %TLC (mid point of the V_L range where $\dot{V}_{exp}$ during WR_{max} was equal to, or greater than, that during the max-dyn effort). This lung volume is indicated on fig 31 by the dashed lines connecting the pressure-volume and flow-volume loops. An $ANOVA_{rm}$ of P_{es} measures indicated that pressure was greater during WR_{max} than WR_{mx-1} under on-mp conditions (11.5 ± 1.92 vs 4.9 ± 1.07 cmH_2O; $p<0.05$), but not under off-mp conditions (2.8 ± 1.16 vs 0.4 ± 0.94 cmH_2O; $p>0.05$). An $ANOVA_{rm}$ of $\dot{V}_{exp}$ at this volume indicated that flow under on and off-mp conditions was significantly greater during WR_{max} measures than during WR_{mx-1} measures (4.5 ± 0.29 vs 4.0 ± 0.27; $p<0.05$).

Had P_{es} increased in the time between WR_{mx-1} and WR_{max}, without a corresponding increase in $\dot{V}_{exp}$, it is clear that P_{maxeff} would have been exceeded. However, $\dot{V}_{exp}$ did increase indicating that, if P_{maxeff} had been exceeded, it could not have been by more than the difference in P_{es} between WR_{mx-1} and WR_{max}

(6.6 ± 1.5 cmH_2O on-mouthpiece; 2.4 ± 1.2 cmH_2O off-mouthpiece).



<u>Fig 31</u> Between-subject pressure and flow-volume loops recorded immediately prior to cessation of maximal exercise (WR_{max}) and approximately 90s earlier (WR_{mx-1}). Comparisons were made at 47 %TLC. Significant increase in pressure or flow between WR_{mx-1} and WR_{max} are indicated by *.

Discussion

The evidence that P_{maxeff} was not exceeded supports previous findings by Olaffson and Hyatt (1969), who compared esophageal pressure measured during exercise to resting measures of P_{maxeff}. Their findings indicated that, even at maximal exercise, P_{maxeff} was not exceeded. A potential source of error in their study was that P_{maxeff} was measured at rest and may not have reflected conditions during exercise, when some degree of bronchodilation may have occurred (Kagawa and Kerr, 1970).

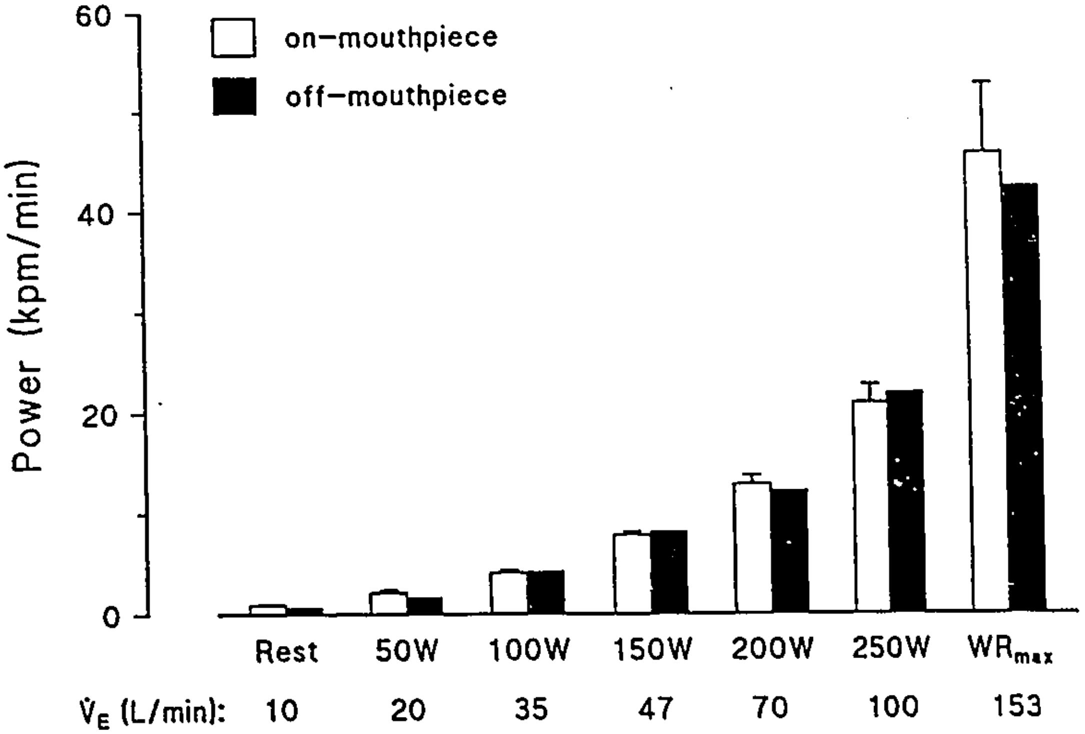
WORK OF BREATHING DURING EXERCISE

Total work of breathing

Measures of the total power of breathing (i.e. positive and negative work performed by both the inspiratory and expiratory muscles) made at rest and at each exercise level are illustrated in fig 32. Power measured under on and off-mp conditions are included. On-mp measures do not include work required to overcome mouthpiece/pneumotachometer resistance. Due to the variability in off-mp measurement of V_L, it was not possible to calculate power for each individual subject under off-mouthpiece conditions and the off-mouthpiece power values included in fig 32 were calculated using the between-subject average results. Statistical comparison of the power measured under on and off-mp conditions was therefore not possible. Inspection of fig 32 suggests however that the power was similar under on and off-mp conditions. As expected, $ANOVA_{rm}$

of the on-mp data showed that the power of breathing increased significantly with each increase in WR ($p < 0.05$).

In fig 33, the total power of breathing measured in this study under on-mouthpiece conditions is compared with previously reported results.



<u>Fig 32</u> Total power required for breathing under on and off-mp conditions. On-mp measures are based on within-subject average data, Off-mp measures based on between-subject average data.

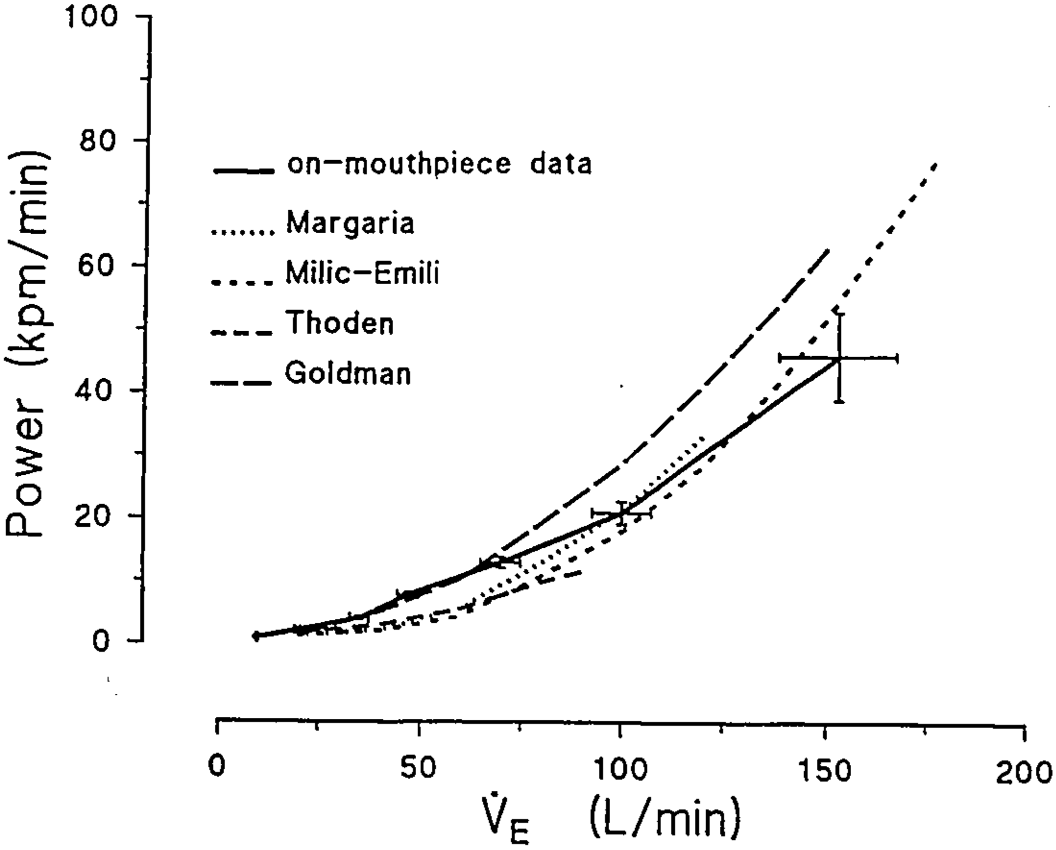


Fig 33 Total power required for breathing under on-mp conditions compared to measures by previous investigators. Measures made by all previous investigators include work performed against equipment resistance. Measures of Margaria et al. (1960) include estimate of power required for distortion of respiratory system.

Discussion

Work of breathing was measured during exercise using the pressure-volume integration method of Rohrer (1925), as adapted by McIlroy et al. (1954) and used by subsequent investigators (Margaria et al.1960; Milic-Emili et al.1962; Thoden et al.1969; Goldman and Mead, 1973). Several changes in the method have permitted a more detailed analysis of the partitioning of work than was possible in these earlier studies. Estimation of R_w (Barnas et al.1987; Barnas et al.1989) has allowed inclusion of the work done in overcoming chest wall resistance. The use of inductance plethysmography has allowed measurement of work under off-mp conditions. Finally, computerization of the technique for calculating work of breathing has made it easier to partition total work into inspiratory/expiratory and resistive/elastic components.

The power of breathing associated with a given level of exercise $\dot{V}_E$ in this study was similar to measures by previous investigators (Margaria et al.1960; Milic-Emili et al.1962; Thoden et al.1969; Goldman and Mead, 1973) (see fig 33). The measures of power at WR_{max} are lower than those made by Milic-Emili et al. (1962) at similar levels of $\dot{V}_E$. This is due, in part, to the inclusion by those authors of work done on the mouthpiece and spirometer, which accounted for approximately 15% of the total work at a $\dot{V}_E$ of 160 L/min, but was almost negligible at lower levels. Inclusion of the estimate of R_w in the current study, did not result in total power measures different than those made in previous studies (fig 33). This is not surprising, as power required to overcome R_w accounted for approximately 10% of the total at all WR.

The results presented in fig 32 do not indicate any difference in the work of breathing under on and off-mp conditions. This lends support to previous studies, where measures made under on-mp conditions were assumed to reflect the work associated with spontaneous breathing (Margaria et al.1960; Milic-Emili et al.1962; Thoden et al.1969; Goldman and Mead, 1973).

Power measured in this study, as well as that measured in previous studies (Margaria et al.1960; Milic-Emili et al.1962; Thoden et al.1969) is less than measures made by Goldman et al. (1976), when they attempted to account for distortion of the chest wall. No attempt was made to account for distortion in the current study.

The technique employed by Goldman et al. (1976) which includes an attempt to account for chest wall distortion has been described in the introduction. This technique requires measuring the extent to which pressure-volume relationships of the abdomen and rib cage during breathing differ from those during relaxation. Inherent in this technique is the assumption that the estimates of rib cage and abdominal compartment volumes are accurate. Goldman et al. (1976) used changes in A-P diameter of both compartments to estimate volume changes. In order to determine the relationship between A-P diameters and volumes of each compartment, subjects were required to perform isovolume and relaxation procedures while changes in lung volume were simultaneously monitored using spirometry. These calibration procedures were performed following a 5 minute recovery period after each level of exercise. If any change had occurred in the relationship between A-P diameters and compartment volumes during this time, errors would have been introduced into their measures of work. As discussed earlier, the current studies and those of Sharratt et al. (1987) have shown that the relationship between the summed inductance plethysmograph signal (proportional to the sum of changes in the diameter of abdominal and rib cage compartments) and lung volume may change quite markedly over the course of exercise. In the current study, these changes occurred in some subjects following the slight movement required for inserting the mouthpiece. Because of these limitations, there is no way to accurately measure the change in the operating volume of the rib cage and abdominal compartments during exercise or any activity where slight postural adjustments might take place.

A further limitation in the technique of Goldman et al. (1976) is the assumption that the rib cage acts as a single compartment, mechanically described by the rib cage A-P diameter vs abdominal pressure relationship during relaxation. The rib cage may be considered to be composed of two compartments, one above and one adjacent to the area of apposition with the diaphragm. The upper compartment is influenced by the pleural pressure adjacent to the lung ($P_{pl,L}$) and the pressure generated by the intercostal muscles. The lower compartment is influenced by the pleural pressure within the area of apposition ($P_{pl,appo}$, which is similar to abdominal pressure), the pressure generated by the intercostal muscles, and the pressure generated by abdominal muscles and diaphragm which insert on the rib cage (Grassino et al.1991). The border between each of these compartments changes throughout the breathing cycle and the magnitudes of all pressures influencing each compartment are not known. Hence, the coupling between rib cage and abdomen remains poorly understood (Grassino et al.1991).

Until these technical and theoretical issues are resolved, the measures made by Goldman et al. (1976) indicating that chest wall distortion accounts for 30% of the total work of breathing should be considered as rough estimates.

The work measured in this study does not include any work performed by simultaneous contraction of inspiratory and expiratory muscles. There is electromyographic evidence that, during increased ventilation, expiratory activity persists into early inspiration (Naus, 1989) and inspiratory activity persists into early expiration (Lopata et al.1977). Simultaneous contraction of inspiratory and expiratory muscles would have opposing effects on P_{es}. Measures of P_{es} made during simultaneous inspiratory and expiratory contractions would only reflect the net effect. Thus, measures of work based on changes in P_{es} do not account for energy expended during simultaneous inspiratory and expiratory activity.

Measures of work presented here were made using values of $P_{el,w}$ predicted from measures made under relaxed static conditions by Knowles et al. (1959). As discussed in the introduction, these measures may not reflect $P_{el,w}$ during breathing. Barnas et al. (1989) have shown that E_w measured using forced oscillations is dependent on the oscillating volume.

Barnas et al. (1989) reported E_w to be approximately 7 cmH_2O when using a forced oscillating volume of 0.75L. Based on figure 6 from that study (Barnas et al.1989), E_w would have been lower with higher tidal volumes. E_w over the range of V_L at which ventilation occurred for the subjects in this study was approximately 5 cmH_2O (based on predictions of $P_{el,w}$ in fig 23). This value is close to what one would predict based on the findings of Barnas et al. (1989).

Inspiratory and Expiratory Components of Work

The inspiratory and expiratory components of muscular power of breathing measured under on-mouthpiece conditions are illustrated in fig 34. This figure includes measures of power made at rest and at all exercise levels including maximal exercise. The majority of the muscular power of breathing under on-mp conditions was inspiratory, but expiratory power played an increasing role as exercise WR (and therefore $\dot{V}_E$) increased. A two way ANOVA$_{rm}$ confirmed that inspiratory power was greater than expiratory power ($p<0.05$), and that both of these increased with exercise work rate ($p<0.05$). This ANOVA$_{rm}$ also indicated an interaction between exercise level and the comparison between inspiratory and expiratory power ($p<0.05$). This interaction suggested a change in the relative division of work of breathing between the inspiratory and expiratory muscles as exercise WR increased. This was further investigated by comparing the fraction of the total power of breathing performed by the expiratory muscles at different exercise levels. Fig 35 illustrates the percentage of the total power of breathing performed by the expiratory muscles. An ANOVA$_{rm}$ of these data indicated a significant effect of exercise WR on this relative measure of expiratory power ($p<0.05$). Post-hoc analysis indicated a significant increase in the relative expiratory power between rest (0.1 ± 0.03%) and 50W exercise (10.5 ± 2.10%) ($p<0.05$), and further increase at 250W and WR$_{max}$ (22.1 ± 2.32% and 26.6 ± 2.89% respectively) ($p<0.05$).

It was not possible to calculate power for individual subjects under off-mouthpiece conditions but, the power measured using the between-subject average results are included in fig 36. It appears that power under on and off-mp conditions was the same.

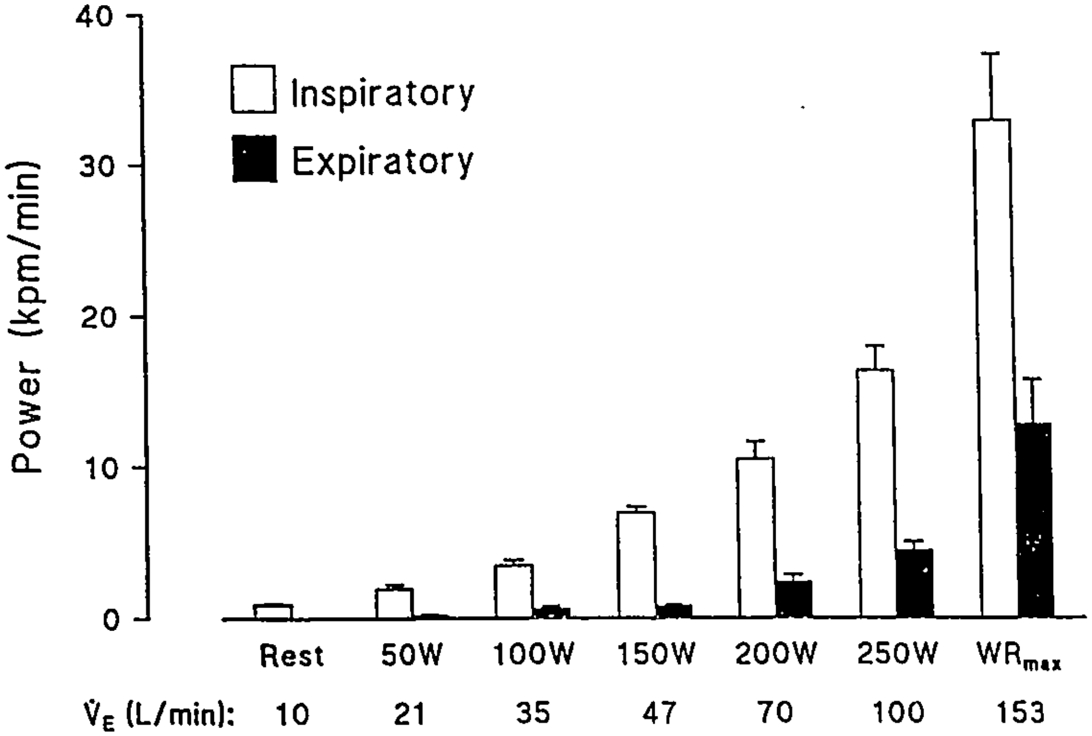


Fig 34 Inspiratory and expiratory muscle power required under on-mp conditions.

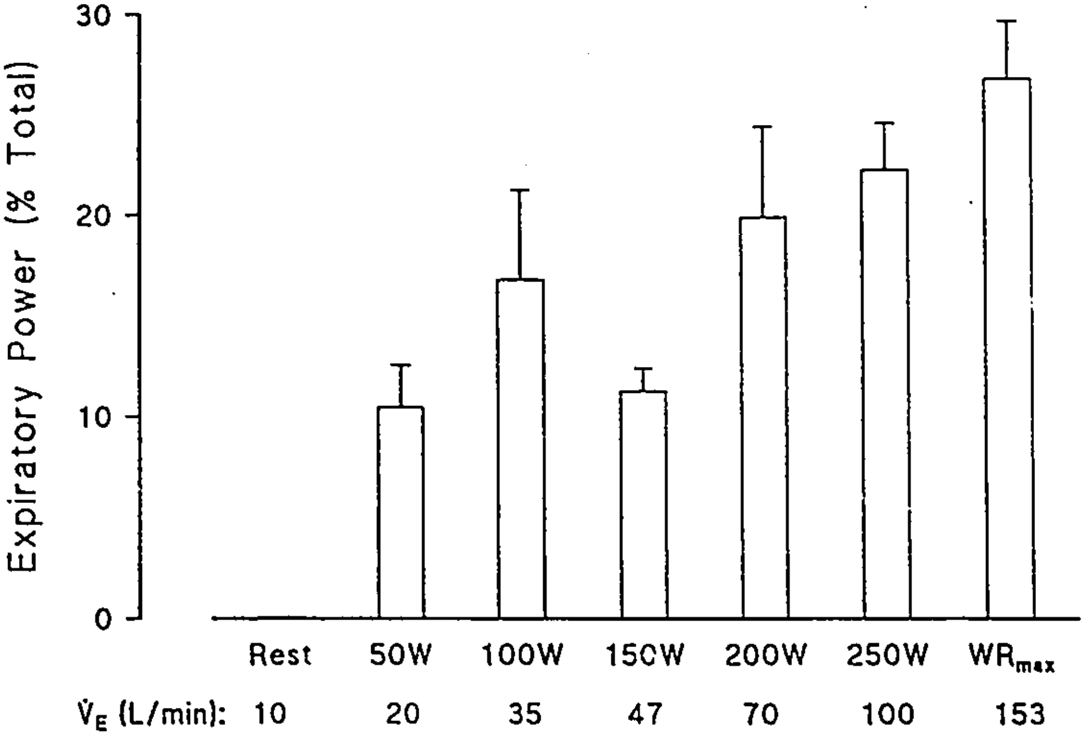


Fig 35 Expiratory muscle power expressed as percentage of total power required for breathing.

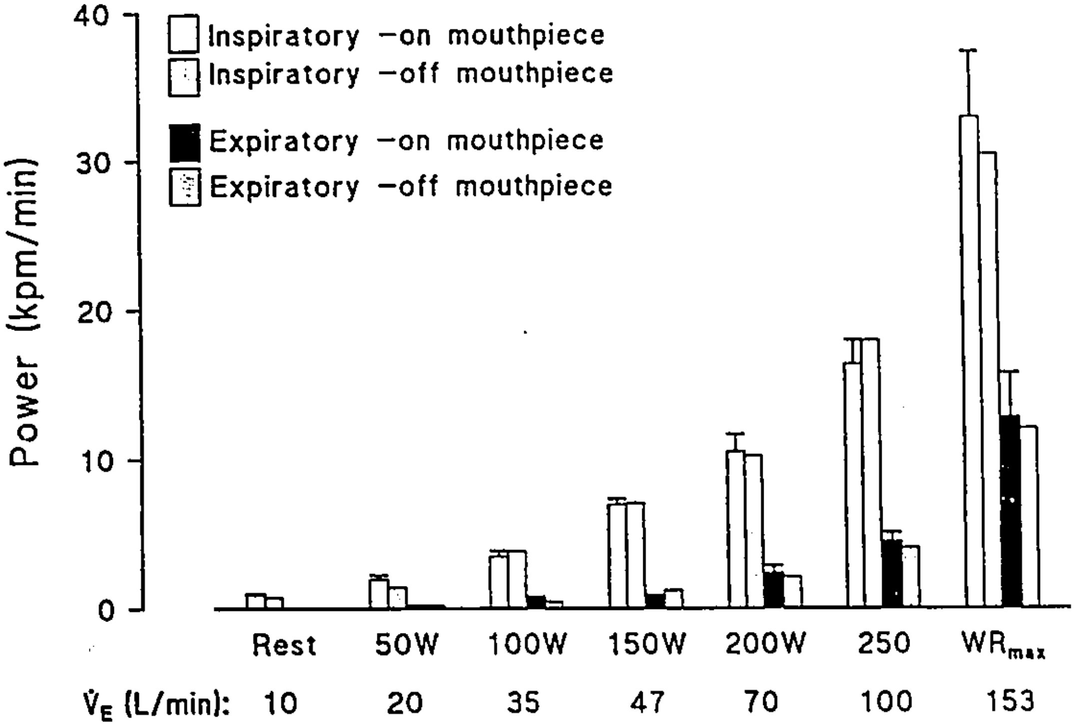


Fig 36 Inspiratory and expiratory muscle power required under on-mp and off-mp conditions. On-mp measures made using within-subject average data. Off-mp measures made using between-subject average data.

Discussion

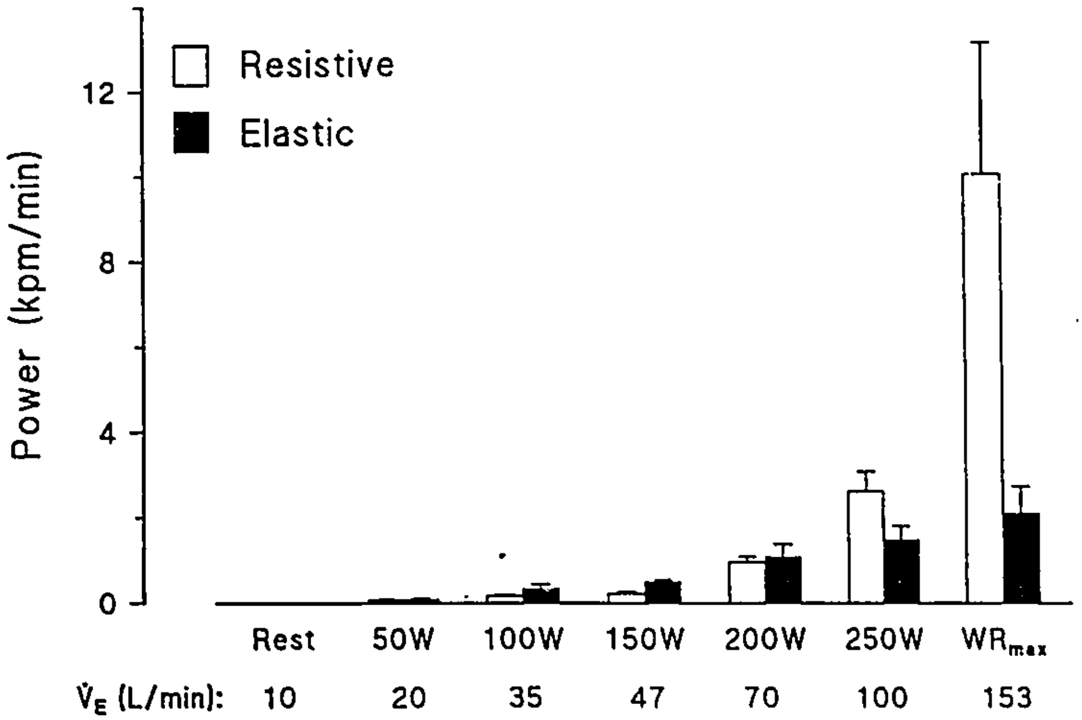
At rest all ventilatory work was performed by inspiratory muscles. At the lowest level of exercise, expiratory activity accounted for 10% of the total work. At maximal exercise, this had increased to approximately 25% of the total work. The only previous study which has partitioned the total work of breathing during exercise into inspiratory and expiratory components is that of Thoden et al. (1969). In that study of normal subjects during treadmill exercise, active expiration was reported to only account for a maximum of 5% of the total work of breathing and only 2.5% at maximal exercise. These authors calculated the work performed by expiratory muscles by measuring the area under the inspiratory and expiratory portions of the esophageal pressure-volume loop. However, no mention is made of measuring/estimating $P_{el,w}$, or absolute lung volume during exercise. Without these measurements, it would have been impossible to determine to what extent P_{es}, measured during expiration, was a result of expiratory muscle activity rather than chest wall recoil.

The findings presented here show that expiratory activity accounts for up to 25% of the work of breathing. The close agreement between on and off-mp results suggests that this is true whether subjects are breathing freely or through a mouthpiece.

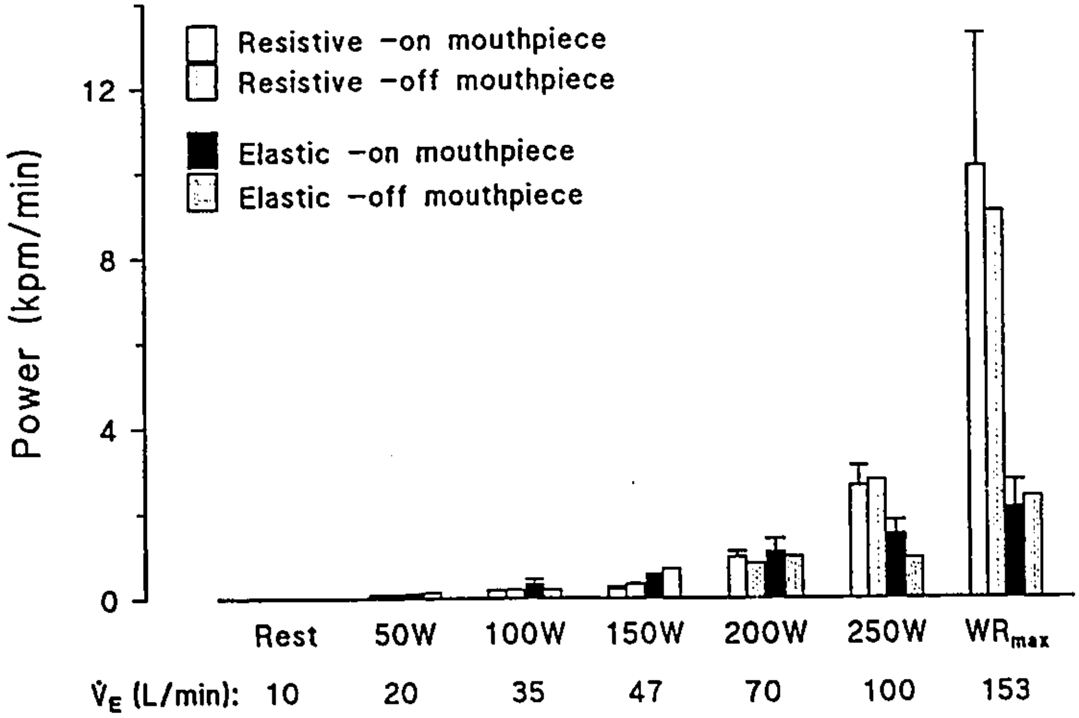
Resistive and Elastic Components of Expiratory Work

This section deals with the partitioning of expiratory work between that required for lowering EELV and that required for increasing $\dot{V}_{exp}$. Comparison between the elastic and resistive components of expiratory power, measured under on-mp conditions are illustrated in fig 37. The elastic component is that needed to overcome the elastic recoil of the chest wall (ie lowering EELV below FRC). The resistive component is that needed to overcome pulmonary and chest wall resistance. These components were analyzed by comparing the fraction of total expiratory power used in overcoming resistance with that used in overcoming elastic recoil. A two way $ANOVA_{rm}$ indicated an interaction between exercise WR and the comparison between relative resistive and elastic power ($p<0.05$). Post-hoc analysis indicated that at 50, 100 and 150W, the relative elastic power exceeded the relative resistive power ($p<0.05$), accounting for 53.45 ± 4.4% of total expiratory power. Between 150W and WR_{max}, there were no significant differences between elastic and resistive power. At WR_{max}, resistive power accounted for 71.01 ± 9.2% of total expiratory power, significantly greater than the 21.44 ± 6.7% accounted for by elastic power ($p<0.05$).

While expiratory power was not measured for individual subjects under off-mp conditions, the resistive and elastic components were determined using the off-mp between-subject average results. In fig 38 these off-mp power values are compared with the on-mp values already presented in fig 37. While statistical analysis of this comparison was not possible, it appears that the changes in resistive and elastic power were the same under on and off-mp conditions.



<u>Fig 37</u> Resistive and elastic power performed by expiratory muscles under on-mp conditions.



<u>Fig 38</u> Resistive and elastic power performed by expiratory muscles under on and off-mp conditions. On-mp power measured using within-subject average data, off-mp power measured using between-subject average data.

Discussion

The role of the expiratory muscles during exercise depends on the exercise level. With low to moderate exercise WR (50 - 150W), most of expiratory power is used to overcome elastic recoil and thus lower EELV below FRC. As exercise WR increases, the power associated with overcoming resistance and therefore increasing expiratory flow becomes relatively more important in determining the total expiratory power, accounting for 71% of this total at WR_{max}.

This is the first study in which the resistive and elastic components of expiratory power have been measured separately. Previous discussions of the use of expiratory muscles during ventilation have emphasized their role in decreasing EELV in order to preserve inspiratory muscle function (Henke et al.1988; Grimby et al.1976; Sackner et al.1980). The current findings indicate that increasing $\dot{V}_{exp}$ is also a major role of expiratory muscle activity during exercise.

THE IMPORTANCE OF ACTIVE EXPIRATION DURING EXERCISE

Active expiration accounts for up to 26% of the total power of breathing during exercise. In this section, an assessment of the importance of active expiration will be made by determining the level of ventilation that could be achieved without any contribution from expiratory muscle. This assessment will be made using the off-mp between-subject average data.

Four pairs of pressure-volume and flow-volume diagrams are presented in fig 39. Those in panel A are the same as those in the off-mp portion of fig 23, and include between-subject average breaths recorded at rest and all levels of exercise. The solid, dark P_{es}-V_L and $\dot{V}_L$-V_L loops in this panel are those recorded at WRmax and therefore represent the ventilation achieved by these subjects while breathing freely at maximal exercise. Also included in the figure is the $\dot{V}_E$ achieved and total power required for breathing ($\dot{W}$) at off-mp WR_{max} (149 L/min and 42 kpm/min respectively).

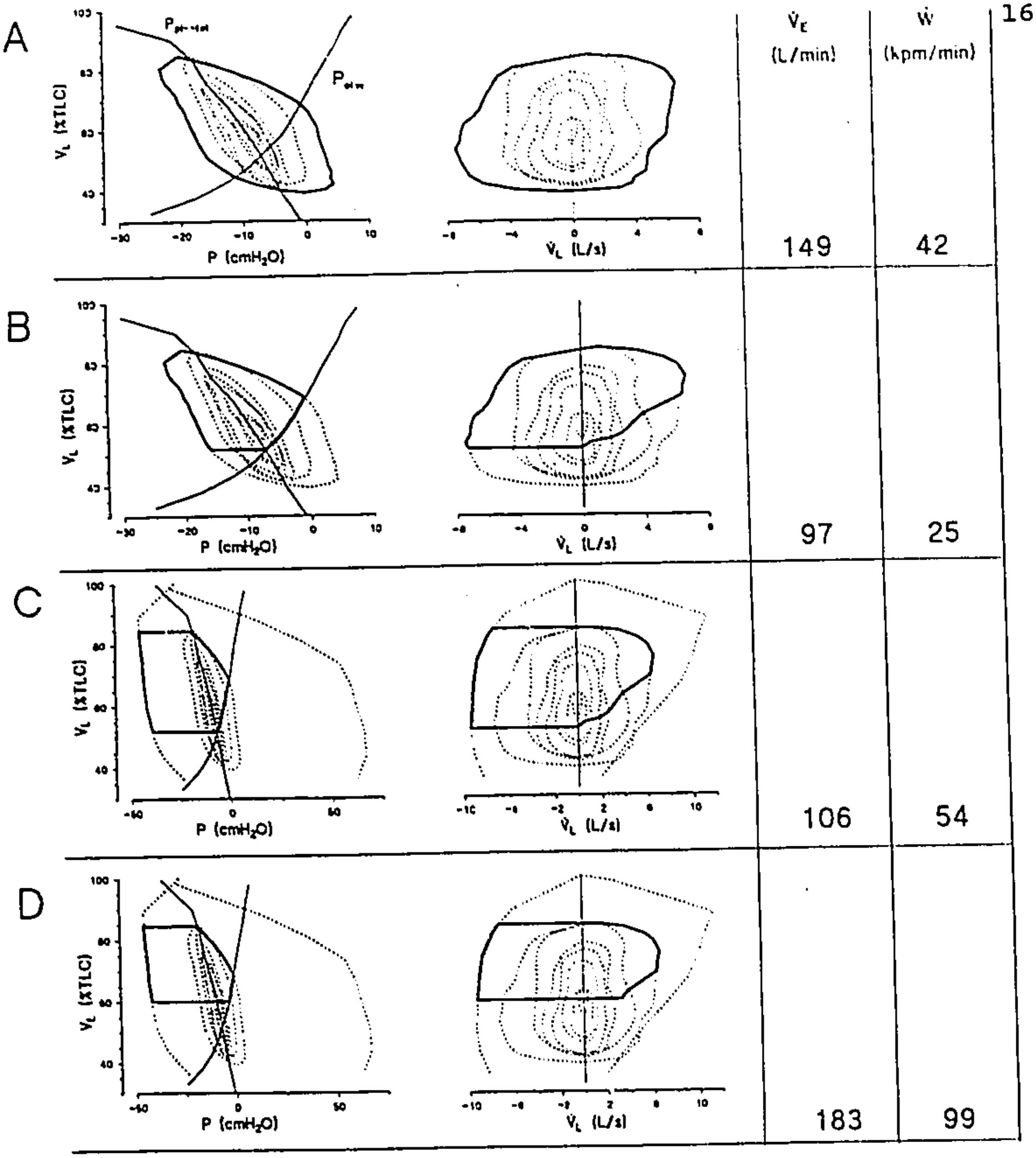


Fig 39 Pressure and flow-volume loops recorded under off-mp WR_{max} conditions, as well as three hypothetical conditions with no expiratory muscle activity. The $\dot{V}_E$ achieved and power ($\dot{W}$) required with each breathing pattern are listed at right. Descriptions of contents of each panel are given in text.

In panel B of fig 39, hypothetical P_{es}-V_L and $\dot{V}_L$-V_L loops are added to those already presented in panel A. These loops, indicated by the solid dark lines, represent a breath which would be taken with the same level of inspiratory effort measured at WR_{max}, but with no active expiration. The expiratory portion of these loops was created by following the WR_{max} loops until the point where the P_{es}-V_L loop reached the $P_{el,w}$ curve. Thereafter, the P_{es}-V_L loop followed the $P_{el,w}$ curve until FRC was reached. The $\dot{V}_L$-V_L loop also followed the WR_{max} loop during expiration until the point where the P_{es}-V_L loop reached the $P_{el,w}$ curve. Thereafter, the $\dot{V}_{es}$-V_L loop progressed such that flow was the same as the flow achieved at each submaximal WR at the V_L where the $P_{el,w}$ curve crossed the P_{es}-V_L loop recorded at the same WR. The inspiratory portions of the hypothetical loops are identical with those measured at WR_{max} except that they begin at FRC. While the power required to breathe in this fashion would be 25 kpm/min, approximately 60% of that used at WR_{max}, the $\dot{V}_E$ would only be 97 L/min. Obviously, if there were no active expiration, some increase in the level of inspiratory activity would be needed in order to reach the levels of $\dot{V}_E$ required at maximal exercise.

In panel C of fig 39, the pressure and flow axes are enlarged, and the maximal dynamic P_{es}-V_L and $\dot{V}_L$-V_L loops recorded at the end of WR_{max} are included. These max-dyn loops do not truly reflect those for off-mp conditions, as they were recorded while the subject breathed in and out of the spirometer. If the resistance of the mouthpiece/spirometer (approximately 0.8 $cmH_2O/L/s$ when $\dot{V}$ = 10 L/s) had not been present during these max-dyn efforts, the pressures achieved would have been smaller by less than 8 cmH_2O (the pressure required to overcome the resistance of the mouthpiece/spirometer).

The dark solid P_{es}-V_L and $\dot{V}_L$-V_L loops in panel C represent a hypothetical breath, with no active expiration and maximal inspiratory effort over the same V_L range as in panel B. The power required for such a breath is approximately the same as for that at WR_{max} but the $\dot{V}_E$ is only 106 L/min. The major reason for the failure with this hypothetical breath to reach the same level of $\dot{V}_E$ as during WR_{max} is the slow flow rate during the later stages of the expiration. In fact, the final 10% of the expiration accounts for almost 50% of the total duration of for the breath. Obviously, without active expiration, even with maximal inspiratory effort, the $\dot{V}_E$ required for WR_{max} could not be achieved unless the EELV were above FRC.

In panel D of fig 39 the solid dark loops again represent an hypothetical breath taken with no active expiration, and maximal inspiratory effort but, unlike the breath in panel C, expiration has been terminated at 60 %TLC, rather than FRC. This resulted in a reduction in expiratory time, an increase in breathing frequency and an increase in $\dot{V}_E$ to 183 (L/min), which is greater than that required at WR_{max}. The power required for this breath would be 99 kpm/min, twice that required for the actual WR_{max} breath. The $\dot{V}_E$ required at WR_{max} could be achieved with a breath similar to that in panel D, but with a sub-maximal inspiratory effort. Data required to generate these P-V and $\dot{V}$-V loops are not available in this study but, to achieve the $\dot{V}_E$ required at WR_{max}, without active expiration would require near maximal inspiratory effort.

In the absence of expiratory activity, the ventilatory demands at maximal exercise could not be met without altering operating lung volume. While they could be met with increased end-expiratory lung volume (hyperinflation), this would increase inspiratory muscle work and place the inspiratory muscle at a length disadvantageous to optimal tension development.

At submaximal exercise levels, the required ventilation could be achieved using only inspiratory activity. However, expiratory muscles are activated even with very mild exercise. Clearly, the effects of expiratory muscle activity are important not only for their augmentation of maximum ventilation. The three effects of expiratory muscle activity (increasing length of inspiratory muscle, storing energy in chest wall to be returned during inspiration, and increasing expiratory flow) all result in lower pressure required from inspiratory muscle at a given level of ventilation. The benefits of breathing with lower inspiratory pressure include decreased effort associated with breathing (Killian and

Campbell, 1991) and decreased likelihood of fatigue of the inspiratory muscle (Bellemare and Grassino, 1982).

The expiratory activity required for these effects would itself contribute to the effort associated with breathing and potentially lead to fatigue of the expiratory muscle (Suzuki et al.1991). However, as illustrated in fig 40, the observed magnitude of expiratory pressure is small relative to capacity. In this figure, the esophageal pressures recorded off-mp at rest and WR_{max} are compared to maximal dynamic pressures (measured, in this study at exhaustion) and maximum static pressures (from Agostoni and Fenn (1960)). Also included are the resting measures of P_{maxeff} of Hyatt and Flath (1966). At maximal exercise, the pressure developed by the expiratory muscle is, at most, 20% of the dynamic capacity. By contrast, the inspiratory pressure during maximal exercise reaches 50% of dynamic capacity. It seems likely that, by reducing the pressure required of inspiratory muscle, expiratory activity results in a lower effort of breathing and less likelihood of ventilatory fatigue during exercise than if breathing were an entirely inspiratory activity.

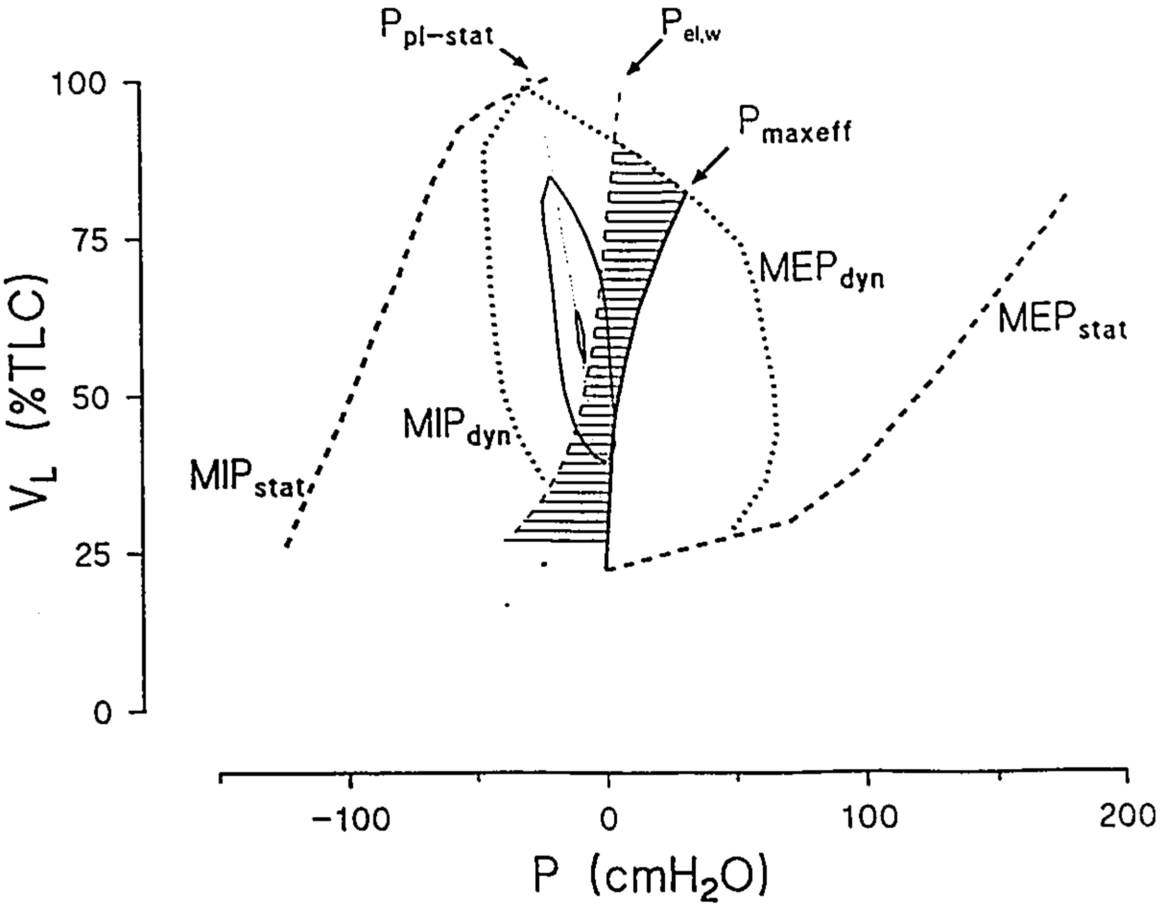


Fig 40 Comparison between pressures developed during breathing and maximal static and dynamic muscle pressures. Solid loops represent average resting and maximal exercise breaths under off-mp conditions. Dynamic pressure capacities are average responses measured immediately following maximal exercise. Static pressure capacities are from Agostoni and Fenn (Agostoni and Fenn, 1960). Also included are P_{maxeff} measures made at rest by Hyatt and Flath (Agostoni and Fenn, 1960)

CONCLUSIONS

The work presented in this thesis was an attempt to reveal the role of expiratory muscle activity during exercise. Mechanical analysis of breathing was performed on normal subjects at rest and during several levels of exercise. A summary of the findings follows:

1/ Mechanical evidence of expiratory activity is found at all levels of exercise. This activity serves two mechanical roles:

A) Lowering of end-expiratory lung volume to a level below functional residual capacity.
With mild exercise, this reduction is approximately 5% of total lung capacity.
With severe exercise, the reduction is approximately 14% of total lung capacity.
It is argued that this reduction in operating lung volume is beneficial, as it lengthens inspiratory muscles, thereby optimizing function, and stores elastic energy which can be recovered during inspiration.

B) Increasing expiratory flow to levels that could not be achieved through passive recoil of the respiratory system alone.

During maximal exercise, peak expiratory flows are approximately 6 L/s. Approximately half of this is attributed to expiratory muscle action.

2/ Expiratory activity accounts for approximately 10% of the total work of breathing during mild exercise. At maximal exercise, this contribution is approximately 26%.

3/ Increases in expiratory esophageal pressure with increasing exercise level are associated with increases in expiratory flow until exhaustion, suggesting that expiratory muscle activity remains effective at all levels of exercise.

4/ Partitioning of the expiratory work of breathing indicates that the role of expiratory activity changes with exercise level.

With mild exercise, most of the expiratory work is used to reduce operating lung volume.

With intense exercise, approximately 70% of expiratory work is used to increase expiratory flow.

5/ Analysis of pressure-volume-flow relationships during maximal exercise and maximal dynamic procedures indicate that the ventilatory demands during maximal exercise probably cannot be met without the contribution of expiratory muscles.

APPENDIX A: COMPUTER PROGRAMS

DIFFERENTIATING OFF-MP PLETHYSMOGRAPH SIGNAL

The following section of a larger program contains the algorithm used for differentiating the plethysmograph volume signal to obtain an estimate of $\dot{V}_L$ for off-mp conditions.

```
    PRINT "This section will integrate of differentiate a  column of"
    PRINT "numbers in a file. You must know how many  columns  there"
    PRINT "are in the file, which column contains time and which one"
    PRINT "you want to treat."
    PRINT:PRINT

    INPUT "Enter the name of the file you want to treat   : ",infile$
    PRINT:PRINT
    INPUT "How many columns are there in this file: ",ncol
    PRINT
    INPUT "Which column do you want to treat: ",trtcol
    INPUT "Which column contains time       : ",timcol
    PRINT
    INPUT "Enter the name of the file you want to write to: ",outfile$
    PRINT:PRINT:PRINT
    PRINT "Do you want to  1/Integrate  2/Differentiate  (1/2): "
    CHOICE$ = INPUT$(1)
    IF CHOICE$ = "1" THEN GOTO 605 ELSE GOTO 606
    PRINT
605 INPUT "Enter the channel with the starting volume: ",VCHAN
606 PRINT
    PRINT "Do you want a sign change? (y/n): "
    SIGN$ = INPUT$(1)
    IF (SIGN$ = "N") OR (SIGN$ = "n") THEN SC = 1 ELSE SC = -1


    OPEN INFILE$ FOR INPUT AS #1
    OPEN OUTFILE$ FOR OUTPUT AS #2
    DIM A(16), B(16), C(16)

610 IF (ROWS > 1) GOTO 612 ELSE GOTO 614
612             FOR I = 1 TO (NCOL +1)
                C(I) = B(I)
         NEXT I

614 IF (ROWS > 0) GOTO 616 ELSE GOTO 620
616             FOR I = 1 TO (NCOL +1)
                B(I) = A(I)
         NEXT I

620 FOR I = 1 TO NCOL
         IF EOF(1) THEN GOTO 640
         INPUT #1, A(I)
    NEXT I

    IF FLAGG = 1 THEN GOTO 621 ELSE VSTART = A(VCHAN):FLAGG = 1
621             ROWS = ROWS + 1

630 IF (ROWS = 2) THEN B(NCOL+1) = VSTART: GOTO 634
    IF (ROWS > 2) THEN GOTO 632 ELSE GOTO 610
```

```
632 IF (CHOICE$ = "1") THEN B(NCOL +1) = C(NCOL + 1) + SC*((B(TRTCOL) * ( A(TIMCOL) - B(TIMCOL) )))
    IF (CHOICE$ = "2") THEN B(NCOL +1) = SC*(( A(TRTCOL) - C(TRTCOL) ) / ( A(TIMCOL) - C(TIMCOL) ))

634 FOR K = 1 TO NCOL-1
          PRINT #2, USING "####.### ";B(K):
    NEXT K
    PRINT #2, USING "####.### ";B(NCOL)
    GOTO 610

640    CLOSE(1):CLOSE(2)
```

WITHIN-SUBJECT AVERAGING

The following section of a larger program contains the algorithm for calculating within-subject average breaths from the three breaths at the end of each collection period.

```
    PRINT "This section will take the output values for"
    PRINT "several consecutive breaths and time average them to"
    PRINT "create one average breath. The inspiratory and expiratory"
    PRINT "times for this breath will be the average of the original"
    PRINT "breaths. The file containing the original breaths should"
    PRINT "be created according to the written instructions."
    PRINT:PRINT
    '***** THIS SECTION WILL SORT FILES ACCORDING TO VOLUME *****

    PRINT:PRINT
    INPUT "Enter the name of the file to be averaged: ",infile$
    INPUT "Enter the name of the file to write to   : ",outfile$

    PRINT "3 values will be averaged and every 3rd will be stored (y/n)"
    Q$ = INPUT$(1)
    IF (q$ = "N") OR (Q$ = "n") THEN GOTO 705 ELSE GOTO 706

705 INPUT "Enter the number of values to be averaged : ",NUM
    PRINT
    INPUT "Every Xth value will be stored, enter X : ",INC
    GOTO 707

706 INC = 2 ' THIS IS HOW OFTEN A VALUE IS PRINTED (should probably be =< num)
    NUM = 3 ' THIS IS HOW MANY VALUES ARE AVERAGED


707 OPEN INFILE$ FOR INPUT AS #1
    OPEN OUTFILE$ FOR OUTPUT AS #2

    J=1:I=1
    DIM  ITIME(600),ETIME(1200),IVOL(600),EVOL(1200),IFLOW(600),EFLOW(1200),IPES(600),
         EPES(1200),IPGS(600),EPGS(1200)
    '***** Read in inspiratory and expiratory arrays *****

    INPUT #1, FLAG,TIME,VOL,FLOW,PES,PGS
    IF FLAG = 0 THEN GOTO 710
    IF FLAG = 1 THEN GOTO 720

710 ' READ IN INSPIRATORY ARRAY

    IF EOF(1) THEN GOTO 730
    TINIT = TIME: KINIT = J
712 ITIME(J)=TIME:IVOL(J)=VOL:IFLOW(J)=FLOW:IPES(J)=PES:IPGS(J)=PGS:J=J+1
    IF EOF(1) THEN GOTO 715
    INPUT #1, FLAG,TIME,VOL,FLOW,PES,PGS
    IF FLAG = 1 THEN GOTO 715 ELSE GOTO 712

715 IMEAN = IMEAN + (ITIME(J-1) - TINIT): ICOUNT = ICOUNT + 1
    FOR K = KINIT TO J-1
      ITIME(K) = (ITIME(K) - TINIT) / (ITIME(J-1) - TINIT)
    NEXT K

    GOTO 720


720 ' READ IN EXPIRATORY ARRAY

    IF EOF(1) THEN GOTO 730
    TINIT = TIME: KINIT = I
722 ETIME(I)=TIME:EVOL(I)=VOL:EFLOW(I)=FLOW:EPES(I)=PES:EPGS(I)=PGS:I=I+1
    IF EOF(1) THEN GOTO 725
    INPUT #1, FLAG,TIME,VOL,FLOW,PES,PGS
    IF FLAG = 0 THEN GOTO 725 ELSE GOTO 722
```

```
725 EMEAN = EMEAN + (ETIME(I-1) - TINIT): ECOUNT = ECOUNT + 1
    FOR K = KINIT TO I-1
      ETIME(K) = (ETIME(K) - TINIT) / (ETIME(I-1) - TINIT)
    NEXT K

    GOTO 710


730 IMEAN = IMEAN/ICOUNT
    EMEAN = EMEAN/ECOUNT




740 '***** Sort inspiratory array *****

    JMAX = J-1
    IMAX = I-1
    FOR COUNT = 1 TO JMAX
       FOR J = 1 TO JMAX-1
         IF (ITIME(J) > ITIME(J+1)) THEN GOTO 742 ELSE GOTO 745
742               BUFF = ITIME(J): ITIME(J)=ITIME(J+1): ITIME(J+1)=BUFF
           BUFF = IVOL(J): IVOL(J)=IVOL(J+1): IVOL(J+1)=BUFF
           BUFF = IFLOW(J): IFLOW(J)=IFLOW(J+1): IFLOW(J+1)=BUFF
           BUFF = IPES(J): IPES(J)=IPES(J+1): IPES(J+1)=BUFF
           BUFF = IPGS(J): IPGS(J)=IPGS(J+1): IPGS(J+1)=BUFF
745    NEXT J
    NEXT COUNT

750 '***** Sort expiratory array *****


    FOR COUNT = 1 TO IMAX
       FOR I = 1 TO IMAX-1
         IF (ETIME(I) > ETIME(I+1)) THEN GOTO 752 ELSE GOTO 755
752        BUFF = ETIME(I): ETIME(I)=ETIME(I+1): ETIME(I+1)=BUFF
           BUFF = EVOL(I): EVOL(I)=EVOL(I+1): EVOL(I+1)=BUFF
           BUFF = EFLOW(I): EFLOW(I)=EFLOW(I+1): EFLOW(I+1)=BUFF
           BUFF = EPES(I): EPES(I)=EPES(I+1): EPES(I+1)=BUFF
           BUFF = EPGS(I): EPGS(I)=EPGS(I+1): EPGS(I+1)=BUFF
755    NEXT I
    NEXT COUNT

    '***** Add inspiratory array onto expiratory array *****

    FOR I = 1 TO IMAX
      ETIME(I) = ETIME(I)*EMEAN
    NEXT I

    J = 1
    FOR I = IMAX +1 TO IMAX + JMAX
     ETIME(I) =(ITIME(J)*IMEAN)+(EMEAN+0.03125)
     EVOL(I)=IVOL(J)
     EFLOW(I)=IFLOW(J)
     EPES(I)=IPES(J)
     EPGS(I)=IPGS(J)
     J=J+1
    NEXT I
    JMAX = JMAX + IMAX

760 ' ***** Average array *****
    COUNT = 1
    J = 1
    FOR J = 1 TO (JMAX - NUM + 1)
    TIME=0:VOL=0:FLOW=0:PES=0:PGS=0
    FOR I = J TO J + (NUM-1)
       TIME = TIME + ETIME(I)
       VOL = VOL + EVOL(I)
       FLOW = FLOW + EFLOW(I)
       PES = PES + EPES(I)
       PGS = PGS + EPGS(I)
       IF (I = (J+NUM-1)) THEN GOTO 761 ELSE GOTO 762
761      TI=TIME/(NUM):VOL=VOL/(NUM):FLO=FLOW/(NUM):PES=PES/(NUM):PGS=PGS/(NUM)
```

```
          IF COUNT = INC THEN PRINT #2,USING "####.### ";TI,VOL,FLO,PES,PGS: COUNT = 0
          COUNT = COUNT + 1
762       NEXT I
     NEXT J

        CLOSE(1):CLOSE(2)
```

BETWEEN-SUBJECT AVERAGING

The following program was used to divide the within-subject average breaths into 40 sections.

```
    INPUT "Enter the name of the file : ",INFILE$
    OPEN INFILE$ FOR INPUT AS #1
    INPUT "Enter the name for output  : ",OUTFILE$
    OPEN OUTFILE$ FOR OUTPUT AS #2
    PRINT
    INPUT "Enter # of cols (5 or 6): ",cols
    PRINT
    INPUT "Enter the subjects TLC (l) : ",TLC
    PRINT
    INPUT "Enter the time at end expiration : ",TEE
    PRINT

    INPUT #1, X1,X2,X3,X4,X5,X6
    PRINT #2, USING"## ###.## ###.### ###.## ###.## ###.## ###.##";1,X1,X2,X3,X4,X5,100*X2/TLC
    CLOSE(1): OPEN INFILE$ FOR INPUT AS #1

    DIM T(500),V(500),X1(500),X2(500),X3(500)
    I=1
10  IF EOF(1) THEN GOTO 20

    IF (COLS = 6) THEN INPUT #1, T(I),V(I),X1(I),X2(I),X3(I),JUNK
    IF (COLS = 5) THEN INPUT #1, T(I),V(I),X1(I),X2(I),X3(I)
    IF T(I) = TEE THEN TM =T(I):VM = V(I):X1M = X1(I):X2M = X2(I):X3M = X3(I):X4M = 100*VM/TLC
    I=I+1
    GOTO 10

20  IMAX = I-1

    TINC1 = TEE/20
    TINC2 = (T(IMAX) - TEE)/20
    J=2:I=1
    TMAX = TINC1

100 IF J = 41 THEN GOTO 200
        IF (T(I) > TMAX-0.00001) THEN GOTO 110
              TSUM = TSUM + T(I)
              VSUM = VSUM + V(I)
              X1SUM = X1SUM + X1(I)
              X2SUM = X2SUM + X2(I)
              X3SUM = X3SUM + X3(I)
              I = I+1:COUNT = COUNT+1
        GOTO 100

110     TT = TSUM/COUNT
        VV = VSUM/COUNT
        XX1 = X1SUM/COUNT
        XX2 = X2SUM/COUNT
        XX3 = X3SUM/COUNT
        VV2 = VV*100/TLC

        IF J = 21 THEN TT = TM:VV = VM:XX1 = X1M:XX2 = X2M:XX3 = X3M:VV2 = X4M
        PRINT #2, USING"## ###.## ###.### ###.## ###.## ###.## ###.##";J,TT,VV,XX1,XX2,XX3,VV2
        TSUM=0: VSUM=0: X1SUM=0: X2SUM=0: X3SUM=0: COUNT=0
        IF (J < 20) THEN TINC = TINC1 ELSE TINC = TINC2
        TMAX = TMAX + TINC
        J = J+1
        GOTO 100

200 PRINT #2, USING"## ###.## ###.### ###.## ###.## ###.## ###.##";J,T(I),X2,X3,X4,X5,100*X2/TLC
    CLOSE(1):CLOSE(2)
```

The following program was used to average together the output from the previous program for all subjects under a given condition, resulting in a between-subject average breath.

```
INPUT "How many files to read in ? : ",FN
PRINT
DIM INFILE$(10),SUMJ(41),SUMV(41),SUMT(41),SUMX1(41),SUMX2(41),SUMX3(41),SUMV2(41)
FOR I = 1 TO FN
PRINT, USING "Enter file name  #";I
INPUT        "                 : ",INFILE$(I)
PRINT
NEXT I
INPUT "Enter the name of the output file : ",outfile$
PRINT:PRINT

FOR I = 1 TO FN
     OPEN INFILE$(I) FOR INPUT AS #1
     FOR  J = 1 TO 41
            INPUT #1, J,T,V,X1,X2,X3,V2
            SUMJ(J) = SUMJ(J) + J
            SUMT(J) = SUMT(J) + T
            SUMV(J) = SUMV(J) + V
            SUMX1(J) = SUMX1(J) + X1
            SUMX2(J) = SUMX2(J) + X2
            SUMX3(J) = SUMX3(J) + X3
            SUMV2(J) = SUMV2(J) + V2
     NEXT J
     CLOSE(1)
NEXT I
OPEN OUTFILE$ FOR OUTPUT AS #1

FOR J = 1 TO 41
     MJ = SUMJ(J)/FN
     MT = SUMT(J)/FN
     MV = SUMV(J)/FN
     MX1 = SUMX1(J)/FN
     MX2 = SUMX2(J)/FN
     MX3 = SUMX3(J)/FN
     MV2 = SUMV2(J)/FN
     PRINT #1, USING"## ###.## ###.### ###.### ###.### ###.### ###.###";MJ,MT,MV,MX1,MX2,MX3,MV2
NEXT J
CLOSE(1)
```

WORK OF BREATHING

This program was used to calculate the work of breathing. This version was used for on-mp data. The version for off-mp data was similar, but did not correct for the resistance of the mouthpiece.

```
 ' This program reads in a dynamic compliance file for lung recoil
 ' This program corrects Pes for the resistance of the mouthpiece and should
 ' be used on-mouthpiece files.  It also has been written so that
 ' negative work is calculated using the uncorrected esophageal pressure.


 1      CLEAR
 DIM
VP(50),FP(50),PP(50),PPn(50),VL(50),PL(50),VW(50),PW(50),V(150),Ppl(150),Ppln(150),iPpl(150),El(150),
    Ecw(150),Rcw(150),iRcw(150)

' **** Read in the filenames
' **** The file with the loop to be analyzed
    INPUT "Enter the initials: ",init$
    INPUT "Enter the WR: ",WR$
    LOOPFILE$ = INIT$ + WR$ + ".41"
    OPEN LOOPFILE$ FOR INPUT AS #1
' **** The file with lung recoil pressures
    CDYNFILE$ =  iNIT$ + "CDYN.P"
    OPEN CDYNFILE$ FOR INPUT AS #2
' **** The file with chest wall recoil
    ECWFILE$ =  INIT$ + "ECW.P"
    OPEN ECWFILE$ FOR INPUT AS #3
' **** The output filename
    OUTFIL1$ = "\junk?\" + INIT$ + WR$ + ".Sm1": OUTFIL2$ = "\junk2\" + INIT$ + WR$ + ".sm2"

    OPEN OUTFIL1$ FOR OUTPUT AS #4
    OPEN OUTFIL2$ FOR OUTPUT AS #5

'        OUTFIL3$ = "\junk\" + INIT$ + WR$ + ".101"
'        open outfil3$ for output as #6

' **** Read in the raw data, get EELV, EILV, FREQ, number of Cdyn and Ecw points

' **** Dynamic loop data
    FOR J = 1 TO 41
         INPUT #1, N, T, VP(J), FP(J), PP(J), JUNK, JUNK
' **** Store the measured pleural pressure for the negative work calculations,
'      and the correct pleural pressure for mouthpiece resistance
          ppn(j) = pp(j)
          if (fp(j) < 0) then pp(j) = pp(j) + (0.7155 * ((-1 * fp(j))^1.5))
          if (fp(j) > 0) then pp(j) = pp(j) - (0.7155 * (fp(j)^1.5))


    NEXT J

    ' **** estimate chest wall resistance for this breath (from Barnas' data)
    EELV = VP(21): EILV = VP(1)
    VT = EILV - EELV
    FREQ = 1/T
    Rescw = -0.4367 - (1.3646 * log(freq)) - (0.5057 * log(vt))
    if (Rescw < 0.49) then Rescw = 0.49
    VE = (EILV - EELV) * freq * 60

' **** Cdyn data
    K = 1
5   IF EOF(2) THEN GOTO 10
         INPUT #2, VL(K), PL(K), JUNK
         K = K + 1
    GOTO 5
10  KMAX = K

' **** Ecw data
```

```
      L = 1
15    IF EOF(3) THEN GOTO 20
           INPUT #3, PW(L), junk, VW(L)
           L = L + 1
      GOTO 15
20    LMAX = L

' **** Establish 100 points for  Dynamic loop Ppl, El, Ecw and Rcw during inspiration

      ' **** Determine volume increment and starting ranges for Ppl, El, Ecw ...

      VINC = (EILV -EELV)/100
      J = 22: K = 2: L = 2

      FOR I = 0 TO 100
           ' **** Establish lung volume at which to determine Ppl,El,Ecw ...
           V(I) = ((EILV - EELV) * (1 - ((100 - I) / 100))) + EELV


30                ' **** Determine if Ppl range is appropriate
           IF (V(I) > VP(J)) THEN J = J + 1: GOTO 30

32         ' **** Determine if El range is appropriate
           IF (V(I) > VL(K)) THEN K = K + 1: GOTO 32

34         ' **** Determine if Ecw range is appropriate
           IF (V(I) > VW(L)) THEN L = L + 1: GOTO 34


           ' **** Determine Ppl at given lung volume, also calculate Ppln, the pleural
           ' **** pressure not corrected for mouthpiece resistance - for -ve work
           Ppl(I) = (V(I) - VP(J-1)) * ( (PP(J) - PP(J-1)) / (VP(J) - VP(J-1) ) ) + PP(J-1)
           Ppln(I) = (V(I) - VP(J-1)) * ( (PPn(J) - PPn(J-1)) / (VP(J) - VP(J-1) ) ) + PPn(J-1)


           ' **** Determine El at given lung volume
           El(I) = (V(I) - VL(K-1)) * ( (PL(K) - PL(K-1)) / (VL(K) - VL(K-1) ) ) + PL(K-1)

           ' **** Determine Ecw at given lung volume
           Ecw(I) = (V(I) - VW(L-1)) * ( (PW(L) - PW(L-1)) / (VW(L) - VW(L-1) ) ) + PW(L-1)

           ' **** Determine Rcw at given lung volume

           Flow = (V(I) - VP(J-1)) * ( (FP(J) - FP(J-1)) / (VP(J) - VP(J-1) ) ) + FP(J-1)
           Rcw(I) =  Ecw(I) - (Rescw * flow)

           ' **** Store inspiratory Ppl and Rcw for .101 file
           iPpl(I) = Ppl(I): iRcw(I) = Rcw(I)

       NEXT I

 ' **** Go through range of volumes again, calculating inspiratory work areas
       FOR I = 1 TO 100

           ' **** Calculate Area A, Chest Wall on Lung Elastance
           IF (Ecw(I) < 0) AND (Ecw(I) >= El(I)) THEN AA = AA + VINC * (0 - Ecw(I))
           IF (Ecw(I) < 0) AND (Ecw(I) < El(I)) THEN AA = AA + VINC * (0 - El(I))

           ' **** Calculate Area B, Chest Wall on Pulmonary Resistance
           IF (Ecw(I) < El(I)) AND (Ecw(I) <  Ppl(I)) THEN AB = AB + VINC * (El(I) - Ppl(I))
           IF (Ecw(I) < El(I)) AND (Ecw(I) >= Ppl(I)) THEN AB = AB + VINC * (El(I) - Ecw(I))

           ' **** Calculate Area C, Chest Wall on Expiratory Muscles (-ve Work)
           ' **** NB this uses, Ppln, which is not corrected for mouthpiece resistance
           IF (Rcw(I) < Ppln(I)) THEN AC = AC + VINC * (Ppln(I) - Rcw(I))

           ' **** Calculate Area D, Chest Wall on Chest Wall Resistance
           IF (Ecw(I) < Ppl(I)) AND (Rcw(I) < Ppl(I)) THEN AD = AD + VINC * (Rcw(I) - Ecw(I))
           IF (Ecw(I) < Ppl(I)) AND (Rcw(I) >= Ppl(I)) THEN AD = AD + VINC * (Ppl(I) - Ecw(I))

           ' **** Calculate Area E, Insp muscles on Pulmonary resistance
```

```
          IF (Ppl(I) < Ecw(I)) AND (Ecw(I) < El(I)) THEN AE = AE + VINC * (Ecw(I) - Ppl(I))
          IF (Ppl(I) < Ecw(I)) AND (Ecw(I) >= El(I)) THEN AE = AE + VINC * (El(I) - Ppl(I))

          ' **** Calculate Area F, Insp Muscles on Lung Elastance
          IF (Ecw(I) >= El(I)) AND (Ecw(I) < 0) THEN AF = AF + VINC * (Ecw(I) - El(I))
          IF (Ecw(I) >= El(I)) AND (Ecw(I) >= 0) THEN AF = AF + VINC * (0 - El(I))

          ' **** Calculate Area G, Insp Muscles on Chest Wall Elastance
          IF (Ecw(I) >= 0) THEN AG = AG + VINC * (Ecw(I) - 0)

          ' **** Calculate Area H, Insp Muscles on Chest Wall Resistance
          IF (Rcw(I) >= Ppl(I)) AND (Ppl(I) >= Ecw(I)) THEN AH = AH + VINC * (Rcw(I) - Ppl(I))
          IF (Rcw(I) >= Ppl(I)) AND (Ppl(I) < Ecw(I)) THEN AH = AH + VINC * (Rcw(I) - Ecw(I))


     NEXT I


' **** Establish 100 points for  Loop Ppl and Rcw during expiration

     ' **** Determine starting range for Ppl
     J = 21: K = 2: L = 2


     FOR I = 0 TO 100


60        ' **** Determine if Ppl range is appropriate
          IF (V(I) > VP(J-1)) THEN J = J - 1: GOTO 60


          ' **** Determine Ppl at given lung volume
          Ppl(I) = (V(I) - VP(J)) * ( (PP(J-1) - PP(J)) / (VP(J-1) - VP(J) ) ) + PP(J)
          Ppln(I) = (V(I) - VP(J)) * ( (PPn(J-1) - PPn(J)) / (VP(J-1) - VP(J) ) ) + PPn(J)

          ' **** Determine Rcw at given lung volume.
          Flow = (V(I) - VP(J)) * ( (FP(J-1) - FP(J)) / (VP(J-1) - VP(J) ) ) + FP(J)
          Rcw(I) = Ecw(I) -(Rescw * Flow)

     NEXT I


     ' **** Go through volumes again, calculating expiratory work areas

     FOR I = 1 TO 100

          ' **** Calculate Area I,Expiratory Muscle on Ecw
          IF (Ecw(I) < El(I)) THEN AI = AI + VINC * (El(I) - Ecw(I))

          ' **** Calculate Area J, Expiratory muscle on Rcw
          IF (Rcw(I) < Ppl(I)) AND (Ecw(I) < Ppl(I)) THEN AJ = AJ + VINC * (Ecw(I) - Rcw(I))
          IF (Rcw(I) < Ppl(I)) AND (Ecw(I) >= Ppl(I)) THEN AJ = AJ + VINC * (Ppl(I) - Rcw(I))

          ' **** Calculate Area K, Lung Elastance on Pulmonary Resistance
          IF (El(I) < Ecw(I)) AND (Ecw(I) < 0) THEN AK = AK + VINC * (Ecw(I) - El(I))
          IF (El(I) < Ecw(I)) AND (Ecw(I) >= 0) AND (Ppl(I) >= 0) THEN AK = AK + VINC * (0 - El(I))
          IF (El(I) < Ecw(I)) AND (Ecw(I) >= 0) AND (Ppl(I) < 0) THEN AK = AK + VINC * (Ppl(I) - El(I))

          ' **** Calculate Area L, Lung Elastance on Inspiratory Muscle (-ve Work)
          ' **** NB this uses Ppln, which is not corrected for mouthpiece resistance
          IF (Ppln(I) < Rcw(I)) AND (Rcw(I) < 0) THEN AL = AL + VINC * (Rcw(I) - Ppln(I))
          IF (Ppln(I) < 0) AND (Rcw(I) >= 0) THEN AL = AL + VINC * (0 - Ppln(I))

          ' **** Calculate Area M, Lung Elastance on Chest Wall Resistance
          IF (Rcw(I) < 0) AND (Ppl(I) < 0) AND (Rcw(I) < Ppl(I)) THEN AM = AM + VINC * (0 - Ppl(I))
          IF (Rcw(I) < 0) AND (Ppl(I) < 0) AND (Rcw(I) >= Ppl(I)) THEN AM = AM + VINC * (0 - Rcw(I))

          ' **** Calculate Area N, Chest Wall on Inspiratory Muscles (-ve Work)
          ' **** NB this uses Ppln, which is not corrected for mouthpiece resistance
          IF (Rcw(I) >= Ppln(I)) AND (Ppln(I) >= 0) THEN AN = AN + VINC * (Rcw(I) - Ppln(I))
          IF (Rcw(I) >= 0) AND (Ppln(I) < 0) THEN AN = AN + VINC * (Rcw(I) - 0)
```

```
         ' **** Calculate Area O, Chest Wall on Chest Wall Resistance
         IF (Ecw(I) >= Ppl(I)) AND (Rcw(I) < Ppl(I)) AND (Ppl(I) >= 0) THEN AO = AO +
                                                                  VINC * (Ecw(I) - Ppl(I))
         IF (Ecw(I) >= 0) AND (Rcw(I) < 0) AND (Ppl(I) < 0) THEN AO = AO + VINC * (Ecw(I) - 0)
         IF (Ecw(I) >= Ppl(I)) AND (Rcw(I) >= Ppl(I)) AND (Rcw(I) >= 0) THEN AO = AO +
                                                                  VINC * (Ecw(I) - Rcw(I))

         ' **** Calculate Area P, Chest Wall on Pulmonary Resistance
         IF (Ecw(I) >= 0) AND (Ppl(I) >= 0) AND (Ecw(I) < Ppl(I)) THEN AP = AP +
                                                                  VINC * (Ecw(I) - 0)
         IF (Ecw(I) >= 0) AND (Ppl(I) >= 0) AND (Ecw(I) >= Ppl(I)) THEN AP = AP +
                                                                  VINC * (Ppl(I) - 0)

         ' **** Calculate Area Q, Expiratory Muscle on Pulmonary Resistance
         IF (Ppl(I) >= Ecw(I)) AND (El(I) >= Ecw(I)) THEN AQ = AQ + VINC * (Ppl(I) - El(I))
         IF (Ppl(I) >= Ecw(I)) AND (El(I) < Ecw(I)) THEN AQ = AQ + VINC * (Ppl(I) - Ecw(I))

         ' **** Calculate Area R, Lung Elastance on Chest Wall Elastance
         IF (Ecw(I) < 0) AND (Ecw(I) < El(I)) THEN AR = AR + VINC * (0 -El(I))
         IF (Ecw(I) < 0) AND (Ecw(I) >= El(I)) THEN AR = AR + VINC * (0 -Ecw(I))

    NEXT I

    ' **** Calculate correction to change work from cmH2Oxl/breath to kpm/min
    crec = (freq * 60)/100

    ' **** Calculate inspiratory and expiratory work and correct to kpm/min
    INSW = (AE + AF + AG + AH + AL + AN) * crec
    negINS = (AL + AN) * crec
    RpulmINS = (AE) * crec
    RwallINS = (AH) * crec
    RtotINS = (AE + AH) * crec
    elasINS = (AF + AG) * crec

    EXPW = (AI + AJ + AQ + AC) * crec
    negEXP = (AC) * crec
    RpulmEXP = (AQ) * crec
    RwallEXP = (AJ) * crec
    RtotEXP = (AQ + AJ) * crec
    elasEXP = (AI) * crec
    totW = insW + expW


' **** Print summary work file
freq = freq * 60
freq2 = freq/100 'converts cmH2Oxl/s to kpm/min

PRINT #4, USING " ###.# ##.# ##.## ##.## ##.## ##.## ##.## ##.## ##.## ##.## ##.## ##.##
#.##";VE,freq,totW,INSW,negINS,RwallINS,RtotINS,elasINS,EXPW,negEXP,RwallEXP,RtotEXP,elasEXP


IF EXPW > 0 THEN PRINT #5, USING "###.##  ##.##  ##.##  ##.##      ##.##  ##.##  ##.## ##.##   ##.##";
totW,insW,expW,(expW/totW)*100,RtotExp,(Rtot/expW)*100,elasEXP,(elasEXP/expW)*100,rescw

IF EXPW = 0 THEN PRINT #5, USING "###.##  ##.##  ##.##  ##.##      ##.##  ##.##  ##.## ##.##   ##.##";
totW,insW,expW,(expW/totW)*100,RtotEXP,0,elasEXP,0,rescw


FOR I = 1 TO 5
CLOSE(I)
NEXT I

goto 1
END
```

APPENDIX B: RESPONSE TIMES OF EQUIPMENT

Data was collected for this thesis using a computer acquisition package, sampling at a rate of 32 Hz. Thus, the time between consecutive data points was 0.031 s. Measurement of the response times of all equipment was necessary to determine whether any time corrections were necessary. If the response of any equipment to a square wave change in the measured variable were less than half complete after 0.031 s, then it would be necessary to make a time correction for that signal.

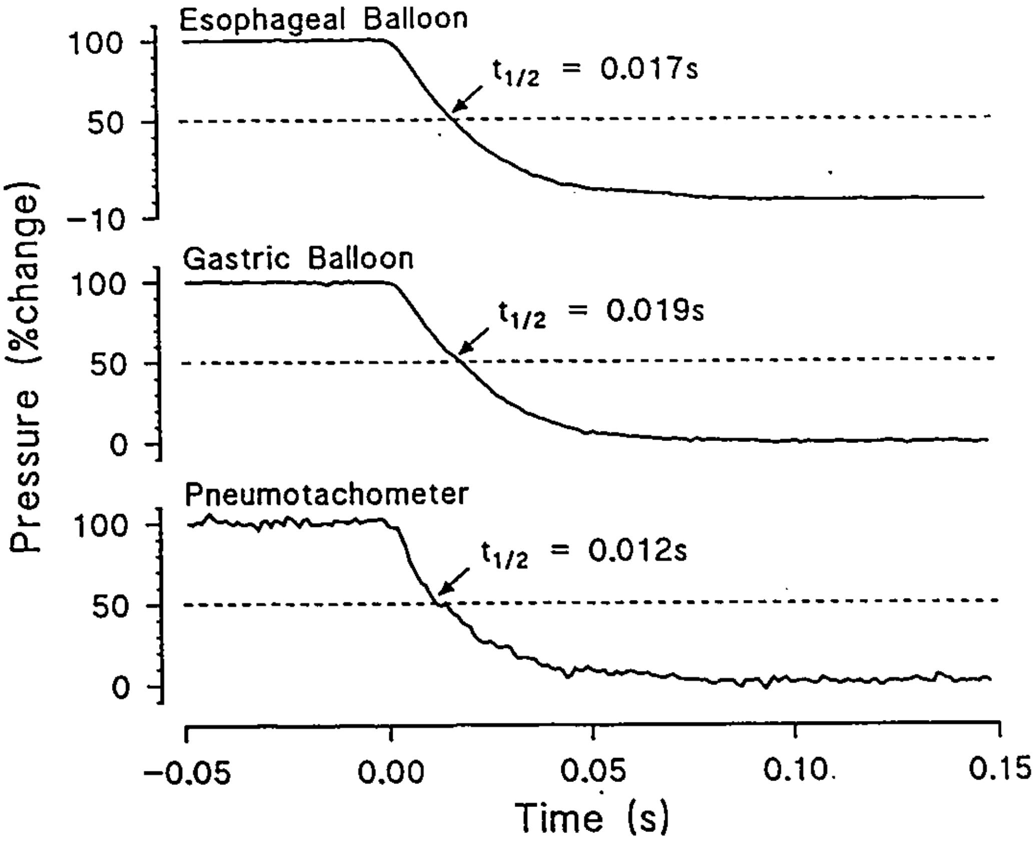
Balloons and Pneumotachometer

The response times of the esophageal and gastric balloons and the pneumotachometer were determined by recording output while they were subjected to a square wave change in pressure. Both the balloons and one of the lines to the pneumotachometer were placed in an elastic balloon, which was then inflated. The output from both balloons and the pneumotachometer were then recorded at 1000 Hz while the elastic balloon was punctured. The three signals recorded during this procedure are presented in fig B1. The half response time ($t_{1/2}$)) was determined as the time after balloon puncture at which the change in pressure was 50% complete. As indicated in this figure, the $t_{1/2}$ for the esophageal and gastric balloon and pneumotachometer were 0.017s, 0.019s and 0.012s respectively.

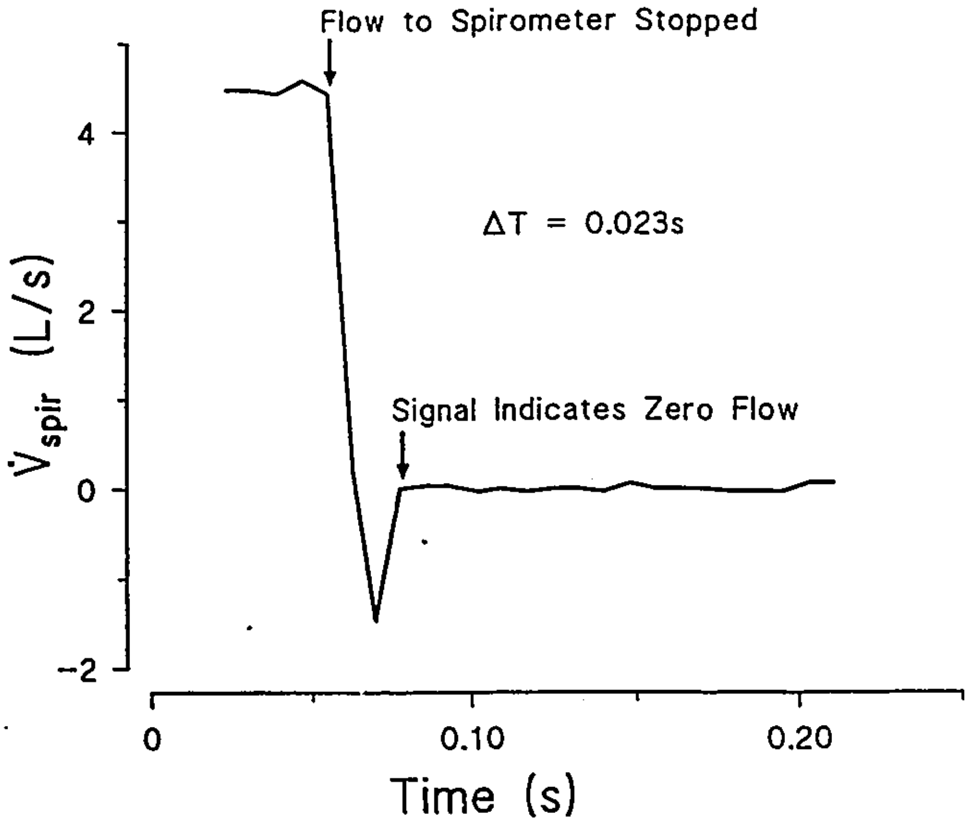
Spirometer

The response time of the spirometer was determined by recording output from the transducer while flow to the spirometer was abruptly stopped. Fig B2 illustrates the differentiated transducer signal, recorded at 64 Hz, while a flow of approximately 4 L/s into the spirometer was abruptly stopped using the pneumatic switching device. The figure indicates that 0.023s after the cessation of flow, the differentiated transducer signal registered zero flow. While the sampling frequency was not high enough to determine the $t_{1/2}$ for the spirometer, it clearly must have been less than 0.023s.

As indicated by these measures, no time adjustments were made for any signals.



<u>Fig B1</u> Time responses of esophageal and gastric balloon and pneumotachometer. Both balloons and one pressure line from pneumotachometer were contained in an elastic balloon which was punctured at 0.00s. $t_{1/2}$ indicates time at which pressure recording had fallen 50% of the way to final plateau.



<u>Fig B2</u> Time response of spirometer. The trace indicates the output from the spirometer/potentiometer while a flow of 4 L/s to the spirometer was abruptly stopped at the time indicated. The time difference between the cessation of flow and the indication of zero flow from the potentiometer was 0.023s.

APPENDIX C: DATA AVERAGING TECHNIQUE

In this appendix, the data averaging technique described in the methods section will be illustrated.

WITHIN SUBJECT AVERAGING

The upper section of fig C1 illustrates the raw data collected under on-mp conditions for subject MI exercising at 250W. Within-subject averaging in all cases was performed on three consecutive breaths, in most cases these were the final three breaths of the collection period. The lower portion of fig C1 illustrates an enlarged view of the three breaths, divided into three inspiratory and three expiratory sections. On the left side of fig C2, the P_{es} V_L and $\dot{V}_L$ signals for each of the three breaths are superimposed and plotted along with the resulting averaged signals. Also on fig C2 are the P_{es}-V_L and $\dot{V}_L$-V_L loops for each of the three breaths, as well as the resulting average loops.

BETWEEN SUBJECT AVERAGING

Between-subject average breathing cycles were created by superimposing and averaging the within-subject average breathing cycles for each subject under each condition. The within-subject average cycles for all subjects exercising at 250W, as well as the resulting between-subject average breathing cycles are illustrated in fig C3. On the left portion of the figure are the P_{es}, V_L and $\dot{V}_L$ responses, on the right are the resulting P_{es}-V_L and $\dot{V}_L$-V_L loops.

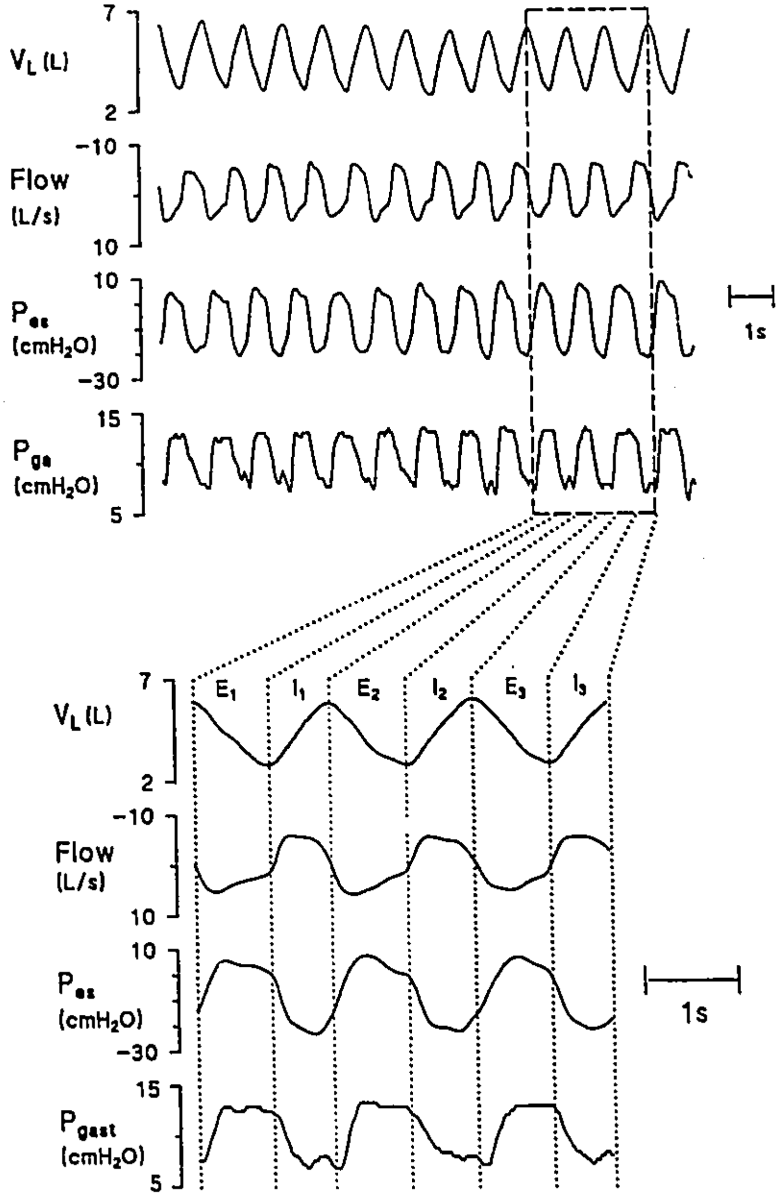


Fig C1 Division of signals into inspiratory and expiratory segments required for within-subject averaging. The upper panel shows the calibrated plethysmograph (V_L), pneumotachometer (Flow) and balloon (P_{es} and P_{ge}) signals. The lower panel shows the final three breaths, divided into three inspiratory and three expiratory segments, which were superimposed and averaged to yield an average breath.

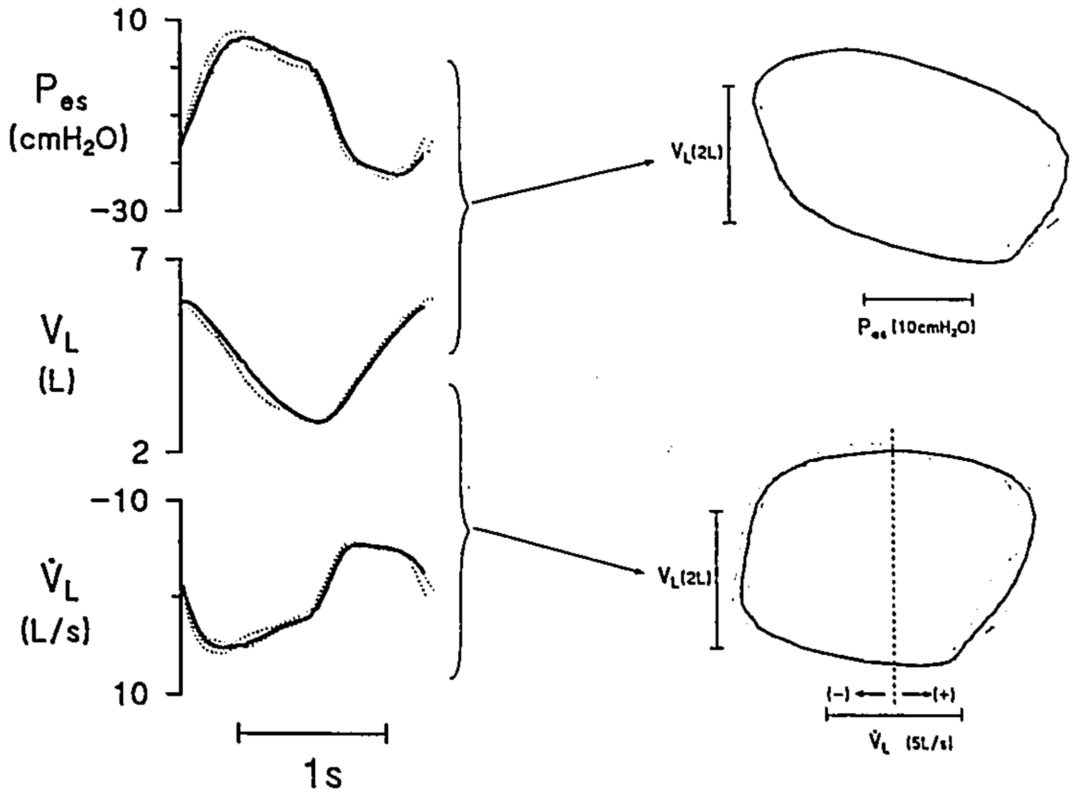
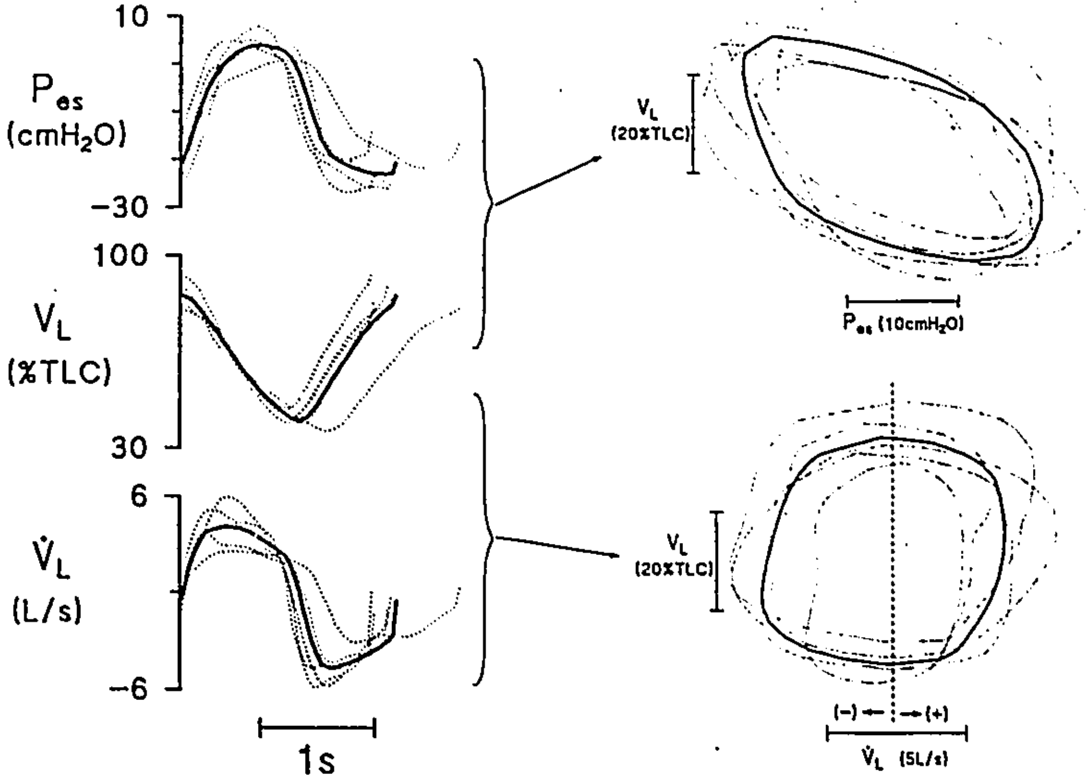


Fig C2 Effects of within-subject averaging. On the left are the P_{es}, V_L and $\dot{V}_L$ signals. Dotted lines represent raw signals for each of the three breaths by subject MI at 250W. Solid lines are the resulting within-subject average. On the right are pressure-volume and flow-volume relationships for both the raw signal (dotted lines) and within-subject average (solid line).



<u>Fig C3</u> Effects of between-subject averaging. On the left are the P_{es}, V_L and $\dot{V}_L$ signals. Dotted lines represent within-subject average signals from each subject at 250W. Solid lines represent the resulting between subject average. On the right are pressure-volume and flow-volume relationships for both the within-subject (dotted line) and between-subject averages (solid line).

APPENDIX D: R EFFECT ON V_L MEASURES

The purpose of this appendix is to investigate the possibility that gas exchange during the He rebreathe procedure resulted in errors in the determination of V_L. In theory, the equations used to determine V_L based on the dilution of He require that the spirometer and thoracic gas volumes are combined as a closed system during the rebreathe procedure. This is not entirely true; oxygen and carbon dioxide continue to diffuse across the alveolar membrane. If the rate at which O_2 leaves the system is different than the rate at which CO_2 enters it, then the volume of the system will change and the F_{He} at the end of the rebreathe will result in an inaccurate V_L calculation. The extent to which this occurs will be determined by examining the steps involved in the calculation of V_L for subject MI during exercise at 320W. This was the highest level of exercise achieved by any subject.

V_L was determined using the following measures:

Initial F_{He} in spirometer (F_1)	= 13.65%
Volume of O_2 added to spirometer (ΔV)	= 4.72L
F_{He} after adding O_2	= 9.19%
F_{He} after subject's 6 breaths (F_3)	= 7.42%

These values were inserted into equation 1:

$$V_{spir} = \Delta V \cdot \left(1 + \frac{F_2}{F_1 - F_2}\right) \tag{1}$$

resulting in a calculation of:

V_{spir} = 14.44L

and then into equation 2:

$$V_L = V_{spir} \cdot \left(\frac{F_2 - F_3}{F_3}\right) \cdot \left(\frac{273 + 37}{273 + T_r}\right) \tag{2}$$

resulting in a calculation of:

$$V_L = 3.62\text{L}$$

To investigate the effects of gas exchange on this calculation, a simultaneous recording of oxygen and carbon dioxide fractions within the spirometer were obtained with the mass spectrometer during the rebreathe. These recordings, as well as the F_{He} and V_{SPIR} are illustrated in fig D1.

The rate at which O_2 was leaving and CO_2 entering the spirometer/thoracic gas volume system was determined by examining the F_{O2} and F_{CO2} traces during the final three breaths of the rebreathe. As illustrated on fig D1, over this period (3.00 sec) F_{O2} decreased by 1.193% while F_{CO2} increased by 1.220%. Thus the volume of O_2 in the system decreased by:

$$0.01193 \cdot (14.44 + 3.62) \cdot \left(\frac{755 - 47}{755}\right) \tag{3}$$

$$= 0.202\text{L}$$
$$= 4.04 \text{ L/min}$$

While the volume of CO_2 in the system increased by:

$$0.01220 \cdot (14.44 + 3.62) \cdot \left(\frac{755 - 47}{755}\right) \tag{4}$$

$$= 0.207\text{L}$$
$$= 4.14 \text{ L/min}$$

When applied over the 10.250 sec duration of the rebreathe, these rates of gas exchange would result in an increase in the spirometer/thoracic gas volume of 0.017L.

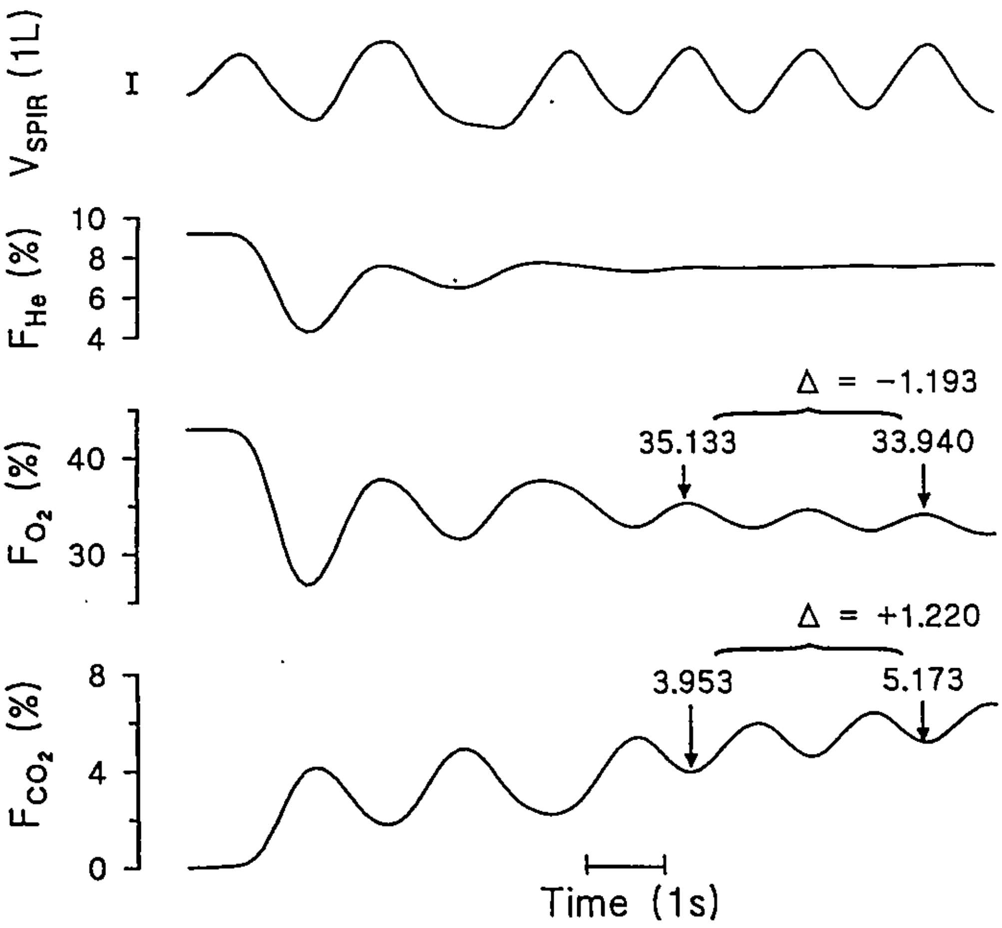
Knowing that the volume of the system increased by 0.017L throughout the rebreathe allows the correction of the post rebreathe F_{He} (F_3)

$$F_{3\text{-corrected}} = F_{3\text{-measured}} \cdot \frac{(14.44 + 3.62)}{(14.44 + 3.62 - 0.017)} \tag{5}$$

= 7.427%

When this corrected value of F_3 is used to calculate V_L using equations 1 and 2 above, the corrected value for V_L is 3.602L. This value is only 0.5% lower than the value of 3.62L calculated without correcting for gas exchange.

The above calculations were repeated using measures made from subject MI at all WR in protocol 1. At rest, the calculated V_L was 0.05% higher than after correcting for gas exchange. The largest error was at 150W, where calculated V_L was 2.0% lower than following correction for gas exchange.



<u>Fig D1</u> Simultaneous tracings of spirometer volume and partial gas fractions of He, O_2 and CO_2 during a helium rebreathe at maximal exercise. The change in the O_2 and CO_2 fractions over the final three breaths (3.00s) are indicated and were used to calculate gas exchange rates.

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