DYSPNEA AND THE MECHANICS OF BREATHING DURING PROGRESSIVE EXERCISE

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A thesis submitted to
the Faculty of Graduate Studies and Research
in partial fulfilment of the requirements for the degree of
Master of Science

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February, 1993

ABSTRACT

This study investigates dyspnea and the mechanics of breathing during progressive exercise Three subject groups, athletes, normal sedentary subjects and chronic obstructive diseased patients were studied during progressive exercise testing to exhaustion on a cycle ergometer Subjects rated dyspnea on a Borg Scale Inspiratory flow, esophageal/gastric pressures and rib cage/abdominal displacements were measured

Subjects demonstrated two patterns of dyspnea response to changes in esophageal (pleural) pressure All athletes, two normals and five patients were termed "low dyspnea responders", (LDR), whereas the remaining subjects were termed "high dyspnea responders", (HDR)

LDR demonstrated large, rapid negative gastric pressure swings, coupled with outward abdominal displacement during early inspiration when compared to HDR, suggesting that LDR utilized abdominal muscle relaxation at the onset of inspiration. This mechanism appears to provide an extra inspiratory force contributing to the increasing pleural pressures required This breathing pattern appears to diminish the sensation of dyspnea at a given pleural pressure.

RESUME

Cette étude examine la dyspnée et les mécaniques de la respiration durant l'exercice progressif Trois groupes sont les athlètes, les normaux sédentaires, ainsi que des patients avec maladie obstructive chronique ont été etudies durant l'exercice progressif maximal Une échelle de Borg était utilisee pour la mesure de la dyspnée Débit respiratoire, pression oesophagienne et gastrique et deplacement de la cage thoracique/abdominale ont aussi été mesurés

Les sujets ont démontré deux types de réponses dyspneiques aux changements de pression oesophagienne Tous les athlètes ainsi que deux normaux et cinq patients étaient classés comme repondants avec tres peu de dyspnée (RPD), tandis que les sujets restants étaient classés comme répondants avec dyspnée importante (RDI)

RPD ont démontré de grands et rapides changements d'amplitude en direction négative de pression gastrique ainsi qu'une augmentation de la circonférence abdominale durant la première partie de l'inspiration comparé aux RDI, suggérant un relâchement des muscles abdominaux dans le groupe RPD au début de l'inspiration Ce mecanisme semble apporter un ajout à la force inspiratoire contribuant ainsi à augmenter la pression pleurale requise Ce patron respiratoire semble diminuer la sensation de dyspnée a tous les niveaux de la pression pleurale

ACKNOWLEDGEMENTS

There are several people I wish to thank, without whose help this thesis would not have been possible. First, I would like to thank my supervisor, Dr. Alex Grassino for his support and guidance throughout the winding road I took in order to complete this study. His patience and help during my full-time Master of Business Administration studies ultimately resulted in the completion of this thesis. Also I would like to thank Dr. Grassino for "encouraging" me to speak at conferences and beer seminars. It was great experience for my present career in the pharmaceutical industry.

I am indebted to Dr. Paul Begin and Christy Wilson, whose help and attendance during the exercise tests was invaluable. I also must thank all of the researchers in our lab at Notre Dame hospital, whose support allowed me to maintain my sanity. Norm Comtois, Christer Sinderby, Adriana Spahija and Doug Wight. I would also like to thank Jennifer Beck for her running around and help getting this thesis finished while I was working full time.

A special thanks also to Adriana, Jennifer and Diane for the translation of the abstract.

I also would like to thank my roommate Penny for putting up with me during the last several horrendous months.

Thanks to everyone at the Meakins-Christie Laboratories and Notre Dame Hospital who made the last many years both memorable and rewarding.

I also want to thank my friends who volunteered as subjects and who endured the dreaded esophageal and gastric balloon catheters. Grant Gush, Richard Young, Steve Gregory and Dave Wilson.

Finally, I would like to thank three people, without whose support and shoulders to lean on this work would not have been possible: my parents and Dave.

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ABBREVIATIONS

AB	Abdomen
A-P	Anterior-posterior
cmH20	centimeters of water
COPD	Chronic obstructive pulmonary disease
EEP	End expiratory pleural pressure
fb	Frequency of breathing
FEV_1	Forced expired volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
HDR	High Dyspnea Responder
IMF	Inspiratory muscle fatigue
l	litre
l/min	litre/minute
l/sec	litre/sec
LDR	Low Dyspnea Responder
min	minute
MIP	Maximum inspiratory pressure
MSV	Maximum sustainable ventilation
MVV	Maximal voluntary ventilation
Pab	Abdominal pressure
P_{cap}	Maximum capacity for pleural pressure generation, adjusted for inspiratory flow and volume
Pdi	Transdiaphragmatic pressure
$\overline{Pdi}$	Mean transdiaphragmatic pressure
Pdi_{max}	Maximum transdiaphragmatic pressure at functional residual capacity with airways closed
$\Delta\overline{Pdi}/Pdi_{max}$	Mean Pdi swing as a fraction of maximum
Pes	Esophageal pressure
ΔPes	Peak to peak esophageal pressure swing
ΔPes/MIP	Peak to peak esophageal pressure swing as a fraction of the maximum inspiratory pressure generated at FRC
$\Delta Pes/P_{cap}$	Peak to peak esophageal pressure swing as a fraction of the maximum capacity to generate pleural pressure
$\overline{Pes}$	Mean esophageal pressure swing
Pes_{max}	Maximum pleural pressure at functional residual capacity with airways closed

$\Delta \overline{Pes}/Pcap$	Mean esophageal pressure expressed as a fraction of the maximum capacity to generate pleural pressure
PFT	Pulmonary function test
Pga	Gastric pressure
ΔPga	Peak to peak gastric pressure swing
Ppl	Pleural pressure
PTI	Pressure-time index
RC	Rib cage
RMF	Respiratory muscle fatigue
RV	Residual volume
sec	second
Ti	Inspiratory time
Te	Expiratory time
T_{tot}	Total time of one breathing cycle
TLC	Total lung capacity
TTdi	Pressure-time index of the diaphragm
TTim	Pressure-time index of the inspiratory muscles
$\dot{V}$	Inspiratory flow
VAS	Visual Analogue Scale
VC	Vital capacity
V_E	Minute ventilation
$\dot{V}_E/FVC$	Minute ventilation normalized as a fraction of the Forced Vital Capacity
$\dot{V}_E/MVV$	Minute ventilation normalized as a fraction of the Maximum Voluntary Ventilation
V_{AB}	Abdominal volume
V_{RC}	Rib cage volume
Vt	Tidal volume
Vt/Ti	Mean inspiratory flow
Vt/Te	Mean expiratory flow
W	Watt

CHAPTER 1 INTRODUCTION

Dyspnea may be defined as breathlessness, difficult or laboured breathing and is a psychophysical sensation which becomes a major debilitating factor for patients suffering from Chronic Obstructive Pulmonary Disease (COPD) Many proposals have been postulated concerning the physiological and psychological causes of dyspnea, however no precise mechanism of dyspnea has been identified to date

Presumably, dyspnea is a sensation resulting from a number of inter-related stimuli For example, the diseased state of the respiratory system in COPD patients may dramatically effect perceived dyspnea The COPD patient may experience overwhelming and exercise limiting dyspnea upon even mild exertion, whereas in normal subjects, exercise is rarely limited solely by dyspnea Only upon extreme, strenuous exercise may dyspnea become a limiting factor for normal subjects

The following presents a summary of the contents of this thesis A relevant literature review is presented in Chapters 2 to 7 inclusively

Chapter 2 will addr_ss the functional anatomy of the respiratory muscles

Chapter 3 discusses Chronic Obstructive Pulmonary Disease and the mechanical limitations it places upon the respiratory system

Chapter 4 will address ventilation during exercise in both normal/athletic subjects and COPD patients, and the mechanics of breathing during exercise

Chapter 5 examines respiratory muscle coordination and the mechanics of breathing and reviews the various methodologies existing for both the quantification and qualification of respiratory muscle activity

Chapter 6 will discuss the scientific field of psychophysics Following a brief historical review, the application of psychophysics to studies of respiration will be discussed

Chapter 7 addresses the specific respiratory perception of dyspnea and examines studies specifically addressing possible stimuli of this sensation

Chapter 8 will discuss the methodology of this study whose first objective was to investigate the relationship between dyspnea and work, ventilation and pressure changes in three distinct subject groups, elite athletes, normal subjects and COPD patients

The second objective of the present study was to examine muscular coordination and respiratory mechanics during progressive exercise testing to determine if a relationship exists to subject's perceived dyspnea

Chapter 9 presents the results of this study.

Chapter 10 will discuss and interpret the results and discuss future areas for investigation

This study attempts to both qualify and quantify parameters contributing to a subjects' subjective sensation of dyspnea Clinically, a better understanding of possible mechanisms of dyspnea is essential for appropriate patient management.

CHAPTER 2 FUNCTIONAL ANATOMY OF THE RESPIRATORY MUSCLES

The thrust of this thesis is on respiratory muscle interaction in health and disease This description of the structure and function of the respiratory muscles provides the basis for future reference

All muscles comprising the respiratory system are skeletal (as any limb muscle), whose primary task is to displace the chest wall, resulting in ventilation of the lungs Functionally, the chest wall can be divided into two compartments mechanically arranged in parallel, the rib cage (RC) and the abdomen (AB), separated from each other by a thin musculotendinous structure, the diaphragm **[1]** Given their arrangement, an increase in lung volume can be achieved by either an increase in RC or AB volume **[1,2] [fig 2.1]**

2.1 The Rib Cage

Structurally, the RC consists of the thoracic vertebrae dorsally, upon which the bony ribs articulate with the transverse processes and vertebral bodies The skeletal arches are completed via costal cartilage and articulations joining the bony ribs to the sternum ventrally The ribs' movement is largely monoaxial (rotation about the axis defined by the ribs' articulations with the vertebral bodies and the transverse processes **[3,4]**), however, given their configuration, rib movement can also occur on a sagittal, frontal or axial plane Mechanically, any muscles which elevate the ribs will provide an inspiratory force, while muscles that lower the ribs will have an expiratory effect **[1]** The horizontal orientation of the upper ribs as well as the more restrictive sternal attachments result in a "pump handle" motion upon inspiration, and movement as a unit with the sternum **[5,6]** In contrast, the lower ribs enjoy greater freedom of movement during inspiration, moving both cranially and laterally in the so called "bucket-handle" pattern

2.2 The Diaphragm

The diaphragmatic fibers radiate from a central tendon to insert peripherally as either the crural (vertebral) or costal portions The diaphragm has been described as an elliptical cylindroid, capped by a dome (the central tendon) **[1,2,7]** The cylindrical portion of the

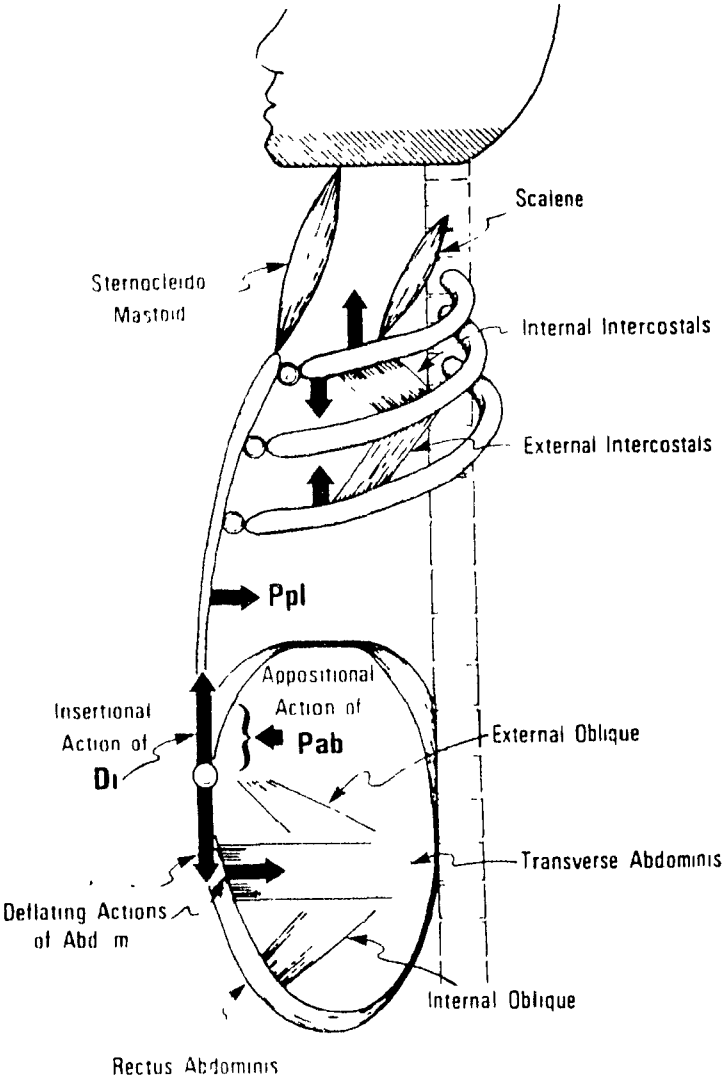


Figure 2 1 Diagrammatic representation of inspiratory and expiratory muscles and their respective actions (arrows)

diaphragm is opposed to the inner aspects of the lower RC, forming the "zone of apposition" **[8,9]**. The zone of apposition, thus, makes the lower RC in effect, a part of the AB container, whose movement is a direct result of changes in abdominal pressure (Pab). As the diaphragm shortens during inspiration, there is a piston-like displacement of the dome related to the axial shortening of the zone of apposition **[9,10]**, with a subsequent expansion of the thoracic cavity. During a quiet inspiration, contraction and descent of the diaphragm thus results in a fall in pleural pressure (Ppl) in the thoracic cavity, an increase in lung volume or decrease in alveolar pressure, depending on whether the airways are open or closed, and an increase in Pab. As the AB is mechanically considered a "liquid filled" container with the majority of its parts considered (ie. bony structures), its movement is largely limited to the ventral abdominal wall and to the diaphragm. Therefore, as Pab increases with diaphragmatic descent, the ventral abdominal wall moves outwards.

The resultant fall in Ppl has an expiratory action on the RC. This is counterbalanced by two inspiratory effects of diaphragmatic contraction upon the lower RC **[8,11,12]**. These are (i) the appositional component, which acts to expand the lower RC and is dependent on the amount of rise of Pab, AB wall compliance and the size of the zone of apposition, and (ii) the insertional component of the costal portion of the diaphragm, which also acts to lift and rotate outwards the lower RC mainly in the transverse direction, resulting directly from the action of the diaphragm at its insertion on the lower six ribs **[7]**. These two forces are active only if the contracting diaphragmatic muscle fibers remain oriented cranially, therefore the abdominal visceral mass acts as a brake to excessive diaphragmatic descent and also as the fulcrum against which the diaphragm pushes to lift the lower ribs **[1,13]**. It has also been demonstrated that the diaphragm has an expiratory action upon the upper RC, directly related to the fall in Ppl incurred during diaphragmatic contraction **[1,14,15]**.

Although authors disagree about the extent to which the diaphragm acts solely to cause the required inspiratory force **[11,16]**, they all seem to agree that the inspiratory effect of the diaphragm is large at low lung volumes **[7]**. However, as lung volume increases, the zone of apposition diminishes, and there is less appositional force acting in the inspiratory direction via the increased Pab. As a consequence, the expiratory action

caused by the increase in the fraction of ribs exposed to Ppl dominates [9,11,12] At extremely high lung volumes (approaching Total Lung Capacity (TLC)), as the zone of apposition disappears, the insertional forces of the diaphragm on the lower RC behave in an expiratory nature [9]

In the normal subject, utilizing the diaphragm as the sole muscle of inspiration would cause distortions of the RC at all lung volumes [1] However, at rest, a uniform expansion of both the upper and lower RC in the anterior-posterior (A-P) diameter and in the transverse diameter of the lower RC is observed This indicates that even during resting breathing, normal humans contract other muscles of the RC to counter the distortional diaphragmatic forces, resulting in a uniform expansion and enhanced A-P diameter of the lower RC and expansion of the upper RC

2.3 The Neck Muscles

2.3.1 Sternocleidomastoid

The sternocleidomastoids originate at the mastoid processes and insert onto the ventral surface of the sternum and medial third of the clavicle In normal subjects, during quiet breathing, the sternocleidomastoids are inactive and therefore not responsible for the upper RC expansion observed at rest However, during high levels of ventilation (ie during exercise), or with inspiratory loading (ie experimental and diseased states), they actively help to cranially displace the sternum and expand the upper RC, predominately in the A-P direction Their activity also results in some transverse expansion of the upper RC [1,17,18]

2 3.2 Scalenes

The scalenes consist of three bundles of muscles, running from the lower five cervical vertebrae to the upper surface of the first two ribs It was previously thought that the scalenes, like the sternocleidomastoids, were only "accessory" muscles of inspiration, becoming actively recruited only as ventilatory demands were significantly increased above resting breathing [17] Today, their role as a primary inspiratory muscle, even at quiet breathing has been recognized [18,19] Their inspiratory activity is to expand the upper

RC mainly in the A-P direction [15], and to cranially displace the sternum [2] The scalenes shorten very little, even during a vital capacity manoeuvre, therefore it appears that the scalenes will maintain their contractile force even at very high lung volumes [18]

2.4 The Intercostal Muscles

There are two distinct muscle layers originating and inserting into the rib cage, the sternum and the spinal processes known as the external and internal intercostals respectively The external intercostals originate from the tubercles of each upper rib dorsally to insert obliquely caudal and ventral to each respective rib below at the costochondral junctions and lay superficial and at right angles to the internal intercostals In contrast, the internal intercostals extend from the sternocostal junctions ventrally to run obliquely caudal and dorsally from the rib above to the rib below to insert into the angles of the ribs [1]

The parasternal muscles are the interchondral portion of the internal intercostals and are the only muscles situated ventrally between the sternum and costochondral junctions [1,7].

Dorsally, the levator costae muscle runs from the transverse processes of the vertebrae cranially to the angle of the ribs caudally After much controversy, it is now accepted that the external intercostal muscles, the levator costae and the parasternals are inspiratory in nature, acting to expand the RC, whereby the interosseous portion of the internal intercostals are expiratory in nature, decreasing RC diameter Selective stimulation of the parasternals in dogs results in an elevation of the ribs, descent of the sternum and subsequently, an increase in lung volume [20] Although the mechanisms of action in man of both the internal and external intercostals are still unclear [21,22], it is believed that through a coordinated mechanism, the internal and external intercostals are able to act in opposite directions on the RC [23,24] Experimentation has also shown that the parasternals are rhythmically active even during quiet inspirations [23,25], while the contributions of the external intercostals and levator costae are limited However, the sternum does move cranially in seated humans during quiet inspiration, indicating that the scalenes counteract the parasternal's action on the sternum

It has been proposed that the intercostals (excluding the parasternals) may play more of a non-respiratory than true respiratory role, namely providing the muscular force for trunk rotation and postural maintenance [26,27]

2 5 Triangularis Sterni

This flat muscle is also known as "transversus thoracis" or "sternocostalis" It lies deep to both the sternum and the parasternal muscles Its action is reciprocal to that of the parasternals, namely a caudal displacement of the ribs with a simultaneous cranial motion of the sternum [28] Activity of the triangularis sterni is not seen in humans during quiet breathing in the supine posture [29], however activity has been observed in standing subjects at rest [30] This muscle is continuously active during expirations below Functional Residual Capacity (FRC) as well as during spontaneous expiratory efforts (coughing, singing, speech) [23,29] It can be assumed that during increased ventilatory demands, eg exercise, the triangularis sterni will become actively recruited along with the internal interosseous intercostals to lower the ribs, increase pleural pressure and to actively force the expiration [23]

2.6 Abdominal Musculature

As previously mentioned, the abdomen is a virtually incompressible liquid-filled container, hence only the diaphragm or ventral abdominal wall can be displaced. The ventral lateral wall is comprised of four main abdominal muscles, whose functions play a major role in respiration [1]

The most ventral of these muscles is rectus abdominis, originating from the ventral aspect of the sternum, the fifth, sixth and seventh costal cartilages and runs along the entire length of the ventral abdominal wall to insert caudally into the pubis The other three muscles form the lateral abdominal wall and their aponeuroses form a sheath about rectus abdominis These are 1) the external oblique which originates from the outer surface of the lower eight ribs (covering both the lower ribs and intercostal muscles) to insert into the iliac crest and inguinal ligament, 2) the internal oblique which lies deep to external oblique and originates from the iliac crest and inguinal ligament and runs cephalically to insert on

the costal margin and also forms an aponeurosis which comprises part of the rectus sheath, and 3) the transversus abdominis which lies the deepest and originates from the inner surface of the lower six ribs and interdigitates with the costal insertions of the diaphragm, and from the lumbar fascia, iliac crest and inguinal ligament Its muscle bulk runs circumferentially about the abdominal viscera to insert ventrally into the rectus sheath [2]

Mechanically, these four muscles act in both non-respiratory functions as the prime flexors and rotators of the trunk and in postural stability as well demonstrating respiratory actions. Two principal actions are displayed by the abdominal muscles in respiration First, their contractions result in an increase in Pab which in turn forces the diaphragm cranially into the thoracic cavity This diaphragmatic ascent increases pleural pressure and (if the glottis is open) decreases lung volume Secondly, contraction of the abdominal muscles also has a direct effect upon the RC Given their insertional attachments to the lower ribs and sternum, contraction of the abdominals should result in a caudal displacement of the lower ribs and subsequent deflation of the RC However, experimentation has demonstrated that abdominal action on the RC is more complex than just a pure insertional, expiratory effect An opposing inspiratory action of the RC has been demonstrated in dogs [22] This "inflation" effect on the RC is directly due to the increase in Pab resulting from abdominal muscle contraction The zone of apposition of the diaphragm permits the direct transmission of Pab to the lower RC Also, when the increased Pab forces the diaphragm cranially, this muscle is stretched, and the resultant passive tension allows the diaphragm to act through its insertional forces to raise the lower ribs [2,22,30]

Although the shape of the RC differs in humans, and therefore insertional forces are different, it is still proposed that the action of the abdominals upon the RC is a balance between the insertional, expiratory force and the inspiratory force related to the rise in abdominal pressure [1] Upon isolation, contraction of the rectus abdominis in humans results in a caudal displacement of the sternum, a significant decrease in the A-P diameter of the lower RC and a small increase in its transverse diameter [31] Contraction of the external oblique in humans causes a small caudal displacement of the sternum and a marked decrease, rather than an increase as seen in the dog, in the RC transverse diameter [31] In humans, the isolated activity of internal oblique and transversus

abdominis have not been demonstrated

The role of the abdominals as expiratory muscles is not disputed, but their role as "accessory" muscles to inspiration is now acknowledged By contracting during expiration, the abdominal muscles can reduce lung volume below the passively determined end-expiratory volume Elastic energy may be stored in the chest wall during expiration, which subsequently could assist the proceeding inspiration [7] Also, the resultant cranial displacement of the diaphragm increases its curvature, decreases its radius and thus allows for a greater generation of pressure for a given tension [7] Abdominal muscle activity during expiration also improves the efficiency of the diaphragm as a pressure generator, improving its ability to expand the lower RC, due to an increase in the size of the zone of apposition [32] The inspiratory muscles are also lengthened to a more favourable operating length, permitting them to generate a given amount of volume with much less activation [7]

It has been demonstrated in the horse [33] and the dog [34,35] that at the end of expiration, the respiratory system is below its resting position and at the onset of the next inspiration, abdominal muscle relaxation allows the diaphragm to descend passively prior to active inspiratory muscle activity In the dog, this passive abdominal relaxation at the onset of inspiration, prior to the onset of inspiratory muscle activity, accounts for 50-60% of that animal's tidal volume (Vt) [36]

In humans, tonic abdominal muscle activity, assumed to be unrelated to respiration, is observed at rest in the standing position [30,37] However, during conditions of CO_2 breathing or inspiratory loading, rhythmic expiratory recruitment of the abdominal muscles is observed [38,39,40]

CHAPTER 3 PATHOPHYSIOLOGY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

3.1 Symptoms and Etiology of COPD

The broad term "chronic obstructive pulmonary disease (COPD)" is traditionally used to describe three specific conditions: chronic bronchitis, asthma and emphysema, all of which are characterized by either chronic expiratory airflow limitations and/or increased airway resistance [41] Established risk factors for COPD include increased age, cigarette smoking, occupational exposures, air pollution and alpha$_1$-antitrypsin deficiency [42].

All patients participating in this study were clinically diagnosed as having chronic bronchitis, emphysema or a combination of both Asthmatics were not studied therefore the following discussion will focus only on the related pathophysiologies, symptoms and limitations associated with chronic bronchitis &/or emphysema

The major complaint of patients with COPD is dyspnea which limits or affects employment and recreation as well as activities of daily living [43]

Diagnosis of COPD is mainly achieved non-invasively by pulmonary function testing (PFT), including spirometry, evaluation of the flow-volume loop and lung volume measurements [44,45] The forced expired volume in one second (FEV_1) is the volume of gas expired in one second following a maximum inspiration [46] and is expressed as the percentage of its predicted value which is based upon the subject's age, sex and height [47] The lower the calculated ratio, usually the more severe the patient's symptoms are The Forced Vital Capacity (FVC) is the maximum amount of air that can be exhaled from the lungs following a maximum inspiration It is effort and time dependent [45] Severity of an obstructive airway disease can be assessed by the FEV_1/FVC ratio An FEV_1/FVC of 80% is normal, 65-79% represents mild impairment, 50-65% indicates moderate impairment and less than 50% represents a severe obstruction to airflow [48] Causes of this airway obstruction include excess mucous in the airways, edema, active broncho-constriction, and loss of lung tissue supporting the airway [49]

Analysis of flow-volume loops demonstrates low flow rates for a given volume in

obstructed patients When maximum expiratory flow is severely reduced, expiratory flow during tidal breathing may reach its maximum level **[50]**

There are also observed changes in lung volumes Functional Residual Capacity (FRC) and Residual Volume (RV) are consistently increased in patients with COPD **[51,52]** and in some patients Total Lung Capacity (TLC) is also increased (severe emphysema) This increase in TLC is mainly due to the large RV measured Resting tidal volumes (Vt) are often reduced, whereas the breathing frequency (fb) is increased, thus maintaining a normal or even higher than average minute ventilation $\dot{V}E$, (greater increase in fb than decrease in Vt) during quiet breathing This pattern of breathing is the result of major adjustments in respiratory muscle activation from the normal pattern [53]

In order to achieve a given volume, large swings in Ppl are required in order to overcome increased airflow resistance and reduced dynamic compliance In an attempt to minimize the negative effects of expiratory flow limitation, COPD patients often have reduced T_I/T_{tot} (duty cycle), to allow more time for expiration **[53]** Expiratory time (Te) is increased at the expense of inspiratory time (Ti) COPD patients also breathe from much higher resting volumes, due to the larger airway size and higher maximum expiratory flows that can be achieved from volumes above FRC [53]

Even though the observed airflow limitation is expiratory in nature, the COPD patient mainly compensates by increasing the work of the inspiratory muscles, observed through the larger inspiratory swings in Ppl This is a compensatory method to not only increase the mean inspiratory flow necessary to sustain a total ventilation when Ti is reduced but also, since breathing is occurring at high lung volumes, it is necessary to overcome the concurrent increase in the elastic work of breathing required to inflate the lungs and chest wall Since more negative Ppl is required to achieve a given tidal volume due to the combined effects of increased airflow resistance, decreased dynamic lung compliance and increased FRC, the inspiratory muscles are forced to chronically work at a higher than normal fraction of their maximum inspiratory force capacity **[54]** Hyperinflation therefore increases the mechanical work of breathing through increases in both the frictional and elastic work required

Severe COPD patients often exhibit marked positive end-expiratory alveolar

pressure since the energy potential developed during inflation is insufficient to return the system to a relaxed end-expiratory equilibrium point This has been termed "auto-PEEP" and provides an added force the inspiratory muscles must overcome before the next inspiration can begin [55]

It has been demonstrated that during hyperinflation, the inspiratory muscles (intercostals and accessories) contract before expiration has proceeded long enough for the lung and chest wall to reach their respective relaxation volumes [56] Therefore, the inspiratory muscles appear to contribute to the increase in FRC and keep the chest at a higher compensatory volume than would occur solely from the airway obstruction [57,58] Also it was found that O_2 consumption of the respiratory muscles in patients of COPD is increased, due to the related distortions of the rib cage caused by hyperinflation, out of proportion to the actual energy required to perform the mechanical work of breathing [59]. The energy cost of breathing is greatly increased for the pressure actually being generated by the breathing effort [55]

3.2 Mechanics of Breathing in COPD

In patients suffering from COPD, accessory muscles of inspiration are often recruited even at quiet breathing [60], however, hypertrophy of sternocleidomastoid or the scalenes are rarely observed

As previously mentioned, the sternocleidomastoids actively contract to raise the sternum and to expand mainly the AP diameter of the upper rib cage [1,17,18] Since the scalene muscles shorten very little, even during full Vital Capacity (VC) manoeuvres, their integrity as a primary inspiratory force is not severely compromised in states of hyperinflation in COPD patients

With hyperinflation, where the patient is breathing at extremely high lung volumes (approaching TLC), the diaphragm becomes flattened, thus, the insertional forces of the diaphragm on the lower rib cage also behave in an expiratory nature [9], drawing the lower ribs inwards Also, the zone of apposition disappears with hyperinflation, therefore, appositional forces in the inspiratory direction are compromised and replaced by expiratory forces due to the higher fraction of lower ribs now exposed to pleural rather than gastric

pressure [9,11,12] As a result, the inspiratory action of the diaphragm is compromised [fig 3 1]

Normally as a muscle shortens, its ability to generate force and tension decreases Therefore, increasing lung volume has a direct effect on the diaphragmatic muscle fibres, affecting their contractile force as the length-tension characteristics of the muscle predicts [61] Lower transdiaphragmatic pressure can be generated for a given tension [55]. During acute hyperinflation which may occur during an asthmatic attack or during high, strenuous exercise, the diaphragm will lose its ability to act as a prime inspiratory force Chronic hyperinflation, however, has been shown to result in chronically shortened diaphragm fibres in hamsters [62,63] Therefore, if an analogy can be drawn, the length-tension characteristics may not play as limiting a role to the ability of the diaphragm to generate tension in a chronically hyperinflated patient as previously thought The insertional force changes will probably become much more significant

Similarly to, but to a lesser degree than the diaphragm [64], severe hyperinflation places the inspiratory intercostals (external, parasternals and levator costae) at a shortened length on their respective length-tension curves Therefore, they become more horizontally oriented losing part of their ' bucket handle" action, resulting in a decrease in the inspiratory activity which the inspiratory intercostals are capable of generating

The role of the abdominal muscles during hyperinflation has also been addressed It has been proposed that the increased abdominal muscle activity during hyperinflation attempts to lengthen the diaphragm and restore it to a more normal resting length Also, upon inspiration, relaxation and therefore outward recoil of the abdominal wall has been demonstrated, acting to lower gastric pressure and facilitate diaphragmatic descent [57] This role of the abdominal muscles as "accessory muscles" of inspiration may attempt to compensate for the added energy costs of the inspiratory intercostal and accessory muscle activity observed during hyperinflation in patients with airway obstruction [57]

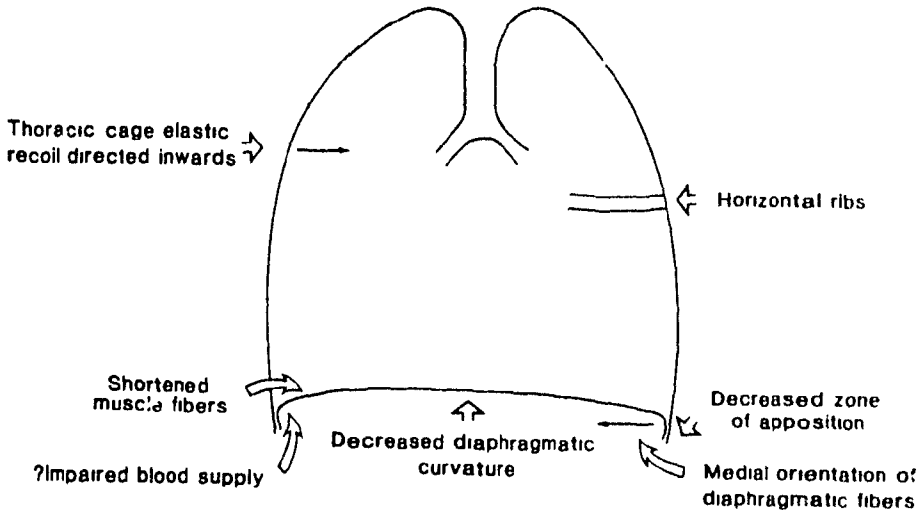


Figure 3.1 The effects of hyperinflation on respiratory muscle function [65]

CHAPTER 4 VENTILATION DURING EXERCISE

The respiratory system can be divided into two major functional components, the lungs themselves, where gas-exchange occurs, and the ventilatory pump. This pump is comprised of the chest wall (rib cage and abdomen), the respiratory muscles, the related controlling centres of the central nervous system and the corresponding neural connections **[66,67,68]**

Exercise causes the metabolic demands of the exercising muscles to increase, therefore placing direct demands upon the respiratory system This increase in metabolic rate results in increased CO_2 production and increased O_2 requirements, demands which are met by the respiratory system by moving larger volumes of air into and out of the lungs **[68]**

Exercise can be classified as static (isometric) or dynamic It has been demonstrated that during static exercise, there is only a small increase in ventilatory demands **[69,70]**, whereas, dynamic exercise imposes much greater demands upon the respiratory system The proceeding study dealt with dynamic exercise testing, therefore it will be further detailed

The increases in ventilatory demand are accomplished through increasing minute ventilation (V_E),

$$V_E = V_t \times f_b \qquad (1)$$

whereby V_t = tidal volume
f_b = breathing frequency

4.1 Ventilatory Responses to Exercise in Normal Subjects

Resting minute ventilation in normal subjects has been shown to be about 10 litres/minute, representing approximately 5% of a normal maximal ventilatory capacity and comprising only 1-2% of the total O_2 consumption of the body **[71,72,73]** The maximum voluntary ventilation (MVV), represents the maximal ventilatory capacity of the respiratory system It has been demonstrated that the MVV can only be sustained for 15-30 seconds, whereas 75% of the MVV can be sustained for about 4 minutes and 60% of the

MVV can be sustained for 15 minutes or longer Thus 60% of the MVV is termed the maximum sustainable ventilation (MSV) Since it is inconceivable for exercise testing to last 30 seconds or less, it is more appropriate to consider the measured VE in relation to the MSV [56,74]

Ventilation has been shown to increase immediately at the onset of exercise [75,76], and during one minute incremental increases in exercise workload, the increase in ventilation is in direct proportion to the increases in CO_2 output, up to the workload where metabolic acidosis is initiated [77] The increase in Vt is achieved through a combination of increasing tidal volume (Vt) and breathing frequency (fb) [68] During light to moderate exercise, most of the increase in Vt is achieved through increasing Vt, accompanied by a progressive increase in fb However, it has been demonstrated that at higher workloads, the increase in Vt is constrained to about 50% of the individual's Forced Vital Capacity (FVC) [78,79,80] and increasing fb becomes the major contributor to the increasing VE with either no further increase or only slight increase in Vt observed [73,80,81] Breathing frequency during maximal exercise is normally about 50 breaths per minute, but this value may be higher in highly trained athletes [82] and at these maximal frequencies, a decrease in Vt may actually be observed prior to the cessation of exercise [75,83] It is believed that this pattern of a Vt of approximately 50% of FVC and an fb of 50 breaths/minute during maximal exercise minimizes the work of breathing, respects the mechanical limitations of the system and provides a sufficient alveolar ventilation to eliminate the CO_2 and maintain homeostasis of arterial blood gases and hydrogen ion concentration [83,84,85,86,87,88,89]

The pressure-volume curve of the respiratory system is such that by increasing Vt predominantly through increases in Vt, the flow-resistive work of breathing is minimized and only when Vt's exceed 75% of Vital Capacity (VC) do increases in the elastic work of breathing become significant [84] The maximum flow volume (MFV) curve also provides constraints which are generally respected during exercise [86,88], however, it has been demonstrated that when some normal subjects reach maximum exercise, expiratory flows may exceed those predicted by the MFV curve [86] It has been suggested that this may be due to a bronchodilation effect of exercise, a change in the elastic properties of the lung

or merely by the incorrect placement of the tidal flow-volume curve during exercise on the volume axis of the resting maximum expiratory flow-volume (MEFV) curve [88].

4.2 Ventilatory Responses to Exercise in COPD Patients

Patients with COPD have similar V_E at rest when compared to normal subjects [90], however, due to reduced airway conductance and reduced respiratory muscle strength, both the MVV and MSV are dramatically decreased [91,92]. It has been shown that the relationship between MVV and MSV is the same in COPD patients as in normals [74], however, given their reduced ventilatory reserve, their resting V_E may account for as much as 40% of the MVV [74,91,93]. Also, the oxygen consumption of the respiratory muscles during quiet breathing has been shown to be about 15% of total body O_2 consumption [71,94]. Thus, the COPD patient can only achieve moderate increases in ventilation during exercise [91,95,96] and these increases in V_E are largely due to disproportionate increases in fb as compared to Vt [97,98,99]. Patients with even moderate degrees of air-flow obstruction have been shown to have expiratory flows which lie on the MEFV curve at quiet breathing [91,97,100], thus the COPD patient is faced with limited strategies to further increase V_E. The patient may shorten inspiratory time (Ti), to allow greater time for expiration, however, this results in a decreased duty cycle (Ti/Ttot) and a large increase in mean inspiratory flow (Vt/Ti) requiring the inspiratory muscles to shorten much more rapidly [68,98]. The second possible strategy is to increase end-expiratory lung volume [97], allowing higher maximum expiratory flows, a more moderate increase in Vt/Ti and preservation of Ti/Ttot [68,98]. This compensation for the limitations of expiratory flow result in much higher inspiratory elastic work requirements as well as an increase in the flow-resistive components of inspiratory work due to the higher Vt/Ti for a given minute ventilation [100]. This second strategy has generally been observed by investigators [89,98,100], but adoption of either the first or second strategy or a combination of both may depend upon the severity of the disease and to the extent of expiratory flow limitation. As in normal subjects, some investigators have observed that COPD subjects can achieve expiratory flow rates during maximum exercise that exceed their resting MEFV curve [91,97], but the accuracy of these results have also been

questioned for the same reasons presented in the previous section concerning normal subjects [89]

4.3 Limitations of Exercise

Normally, the ventilatory system has not been regarded as a limiting factor of exercise in normal subjects; however, in patients with COPD, their severely limited ventilatory capacity will result in a reduced exercise capacity [89,91,93,100,101] Some evidence, though, has been proposed indicating that indeed the respiratory system may somewhat limit exercise in normal subjects at severe workloads Arterial hypoxemia has been observed, during heavy exercise, in some highly trained athletes [102,103,104] These authors suggested that the mechanics of the respiratory system, muscle fatigue or the energetics of respiratory muscles may have set the Vt at a level lower than could have been achieved, since ventilatory reserve still existed, at the cost of arterial hypoxemia [103] It has also been demonstrated that a mechanical constraint to increasing ventilation due to an expiratory flow limitation may exist for normal subjects undergoing heavy exercise since expiratory flows approach or even exceed the maximum expiratory flows as defined by the resting MEFV curve at the end of expiration [86] or achieve maximum values throughout most of expiration [105] In order to further increase their expiratory flows, and thus further increase ventilation, the athletes would be forced to breath at higher lung volumes This hyperinflation would place the now shortened inspiratory muscles at a mechanical disadvantage, increasing the elastic work of breathing, decreasing mechanical efficiency and increasing the vulnerability of the inspiratory muscles to develop fatigue [106] The flow-volume loop limitation to ventilation may thus be valid for normal subjects as it has been shown that exercise ventilation does improve with HeO_2 breathing, possibly through a reduction in the resistive work of breathing [107,108,109] or to an enlargement of the maximal flow-volume loop [110] Another alternative to increasing VE without changing resting lung volume would be to increase inspiratory flow rates, however, studies in normal subjects at high intensities of exercise show that both inspiratory flows and pleural pressures are already close to maximum achievable values [86,105]. Based upon this observation, it has been suggested

that the force-velocity characteristics of the inspiratory muscles may therefore impose a constraint on further increases in inspiratory flows [111]

The above discussion concerning mechanical limitations to exercise also directly applies to patients with COPD, whereby levels of ventilation achieved during exercise often reach the subject's maximum breathing capacity [91,93] and further increases in expiratory flow is limited by maximal flow-volume loop constraints [89,91,93,100] Exercise limitation in COPD subjects is also related to reduced respiratory muscle strength (RMS) [92] Hyperinflation (associated with increases in FRC) is often marked in COPD subjects, resulting in shortening of the inspiratory muscles and diaphragmatic flattening, thereby resulting in decreases in these muscles' contractile forces [61,112] and ultimately decreasing the maximal inspiratory pressures for a given volume that they are capable of generating Other factors such as prolonged inactivity, steroid administration and chronic hypoxemia also weaken RMS in COPD patients [113]

Respiratory muscle fatigue can be defined as "a condition in which there is a loss in the capacity for developing force and or velocity of a muscle in response to a load and which is reversible by rest" [114] Inspiratory muscle fatigue during heavy exercise has been shown in some patients, indicated by electromyographic spectral analysis [115,116,117] and transdiaphragmatic pressure measurements [118]. However, other investigators have failed to observe changes in the electromyographic frequency spectrum indicative of diaphragm fatigue in their exercising COPD patients despite very high pressure generations [119] They also failed to observe any changes in post exercise breathing patterns [120] or increases in the values of the pressure time index of the diaphragm (TTdi) which exceeded the known fatigue threshold [121]

The combination of hyperinflation and further dynamic increases in FRC which occur during exercise in COPD subjects [89,122] forces the inspiratory muscles to operate at a disadvantageous length on the length-tension curve where they are predisposed to developing fatigue [74,106,123,124], however, there is disagreement as to whether inspiratory muscle fatigue does limit exercise

Finally, dyspnea has been shown to significantly limit exercise in COPD patients and in normal subjects exercising at extremely high levels of work.

CHAPTER 5 MECHANICS OF BREATHING AND RESPIRATORY MUSCLE COORDINATION

Mechanically, chest wall behaviour is a function of both the active contractile properties of the respiratory muscles and the passive mechanical properties of the chest wall's major components, that is the rib cage, diaphragm and abdomen Coordination is used to describe the neuromechanical interaction among different respiratory muscle groups as well as between respiratory and non-respiratory muscles [125]

5.1 Historical Development

Early investigators considered the chest wall as a single compartment and studies focused on the static volume-pressure relationship of the respiratory system [126,127] It was assumed that mouth pressure ($P_{el,rs}$) represented the sum of the pressures exerted by the recoil of the chest wall ($P_{el,w}$) and the lung ($P_{el,l}$) The inability to directly measure these pressures, however, posed a major limitation, forcing early investigators to use known in-vitro pressure-volume relationships of the lung to determine $P_{el,w}$:

$$P_{el,w} = P_{el,rs} - P_{el,l} \qquad (1)$$

This limitation was overcome in 1949 with the introduction of the esophageal balloon technique for measuring transpulmonary pressures *in vivo* [128] Now the respiratory system could be partitioned into both its chest wall and lung components

Agostoni and Rahn [129] developed the method for measuring transdiaphragmatic pressure (Pdi), permitting a more complete analysis of the contributions of the thoracic, diaphragmatic and abdominal components to the mechanical behaviour of the respiratory system Pdi was determined by subtracting the gastric pressure (Pga) (measured as an index of abdominal pressure) by the esophageal pressure (Pes) (measured as an index of intrathoracic or pleural pressure) They determined that Pdi could be generated not only by active diaphragmatic contraction but also through the passive stretching of the muscle Measuring Pes and Pga also permitted the quantification of the pressures acting to displace both the abdomen (AB) and the rib cage (RC) [125]

A parallel action of the RC and diaphragm was assumed, leading investigators to assess increases in lung volume as the summation of RC expansion and diaphragmatic descent [130,131,132]

5 2 Analysis of Rib Cage and Abdominal Displacement

Konno and Mead in 1967 hypothesized that the chest wall enjoyed two degrees of freedom, thus changes in lung volume could be accommodated independently through RC or diaphragm-AB displacement **[133]** Using linear differential transducers, the anteroposterior (A-P) displacements of the RC versus the AB were plotted under both active (isovolume manoeuvres) and passive conditions (giving the RC-AB relaxation line) at volumes ranging from residual volume (RV) to total lung capacity (TLC) **[Figure 5.1]** Isovolume manoeuvres are performed when the subject, with glottis closed, alternately contracts his abdominal muscles while simultaneously expanding his rib cage, thus displacing volume from the abdomen into the rib cage, and then relaxing his abdominal muscles and depressing his rib cage, thus displacing volume from the rib cage into the abdomen The result is a series of plotted isovolume isopleths from RV to TLC representing the different configurations and maximum excursions (combinations of rib cage and abdominal wall) that the chest wall can have for any single lung volume

It was proposed that respiratory muscle activity could be inferred from plotting subsequent relative motion diagrams, whereby A-P motion of the RC is plotted versus A-P motion of the AB during breathing, in relation to the plotted relaxation line and isovolume isopleths Any deviations from the relaxation line would require muscular activity Deviations to the left of the relaxation line inferred either inspiratory activity operating on the rib cage, expiratory abdominal activity or a combination of the two, whereas deviations to the right of the relaxation line inferred expiratory muscle activity operating on the rib cage,inspiratory activity operating on the abdomen or some combination of the two **[133]**.

RC and AB displacement during quiet spontaneous breathing was found to lie very close to the respective relaxation line, however it was noted that slight deviations to the right of the relaxation line occurred during inspiration, indicating that some inspiratory activity was operating on the abdomen **[133]** The relative volume changes of the RC and the AB during

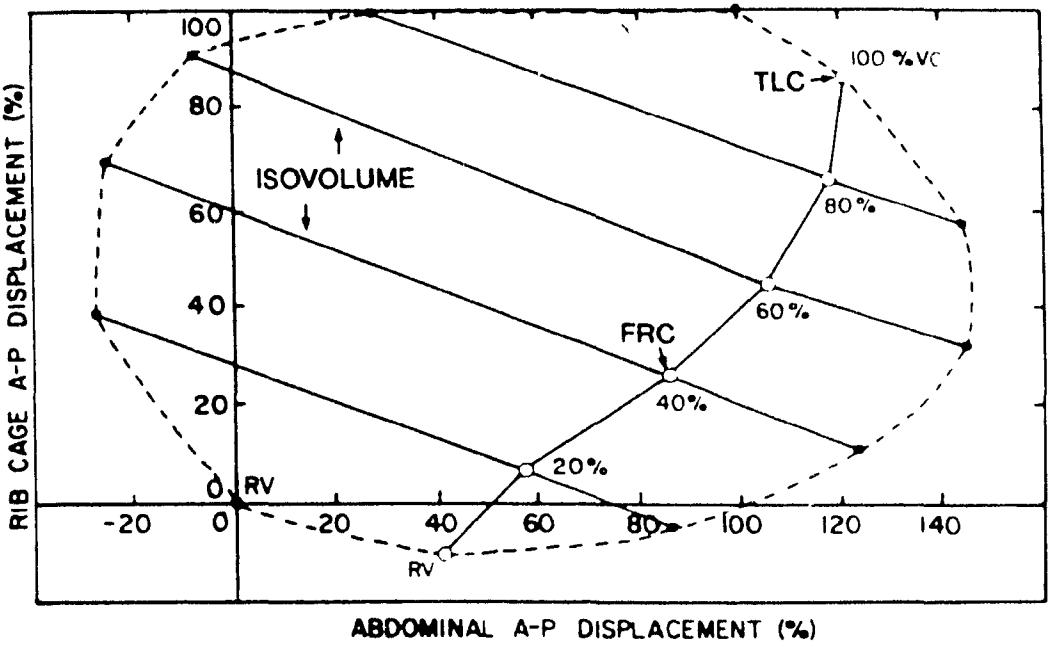


Figure 5.1 Konno-Mead Diagram [134].

increasing ventilation stimulated through hyperventilation [133], re-breathing [135] and exercise [136] demonstrated substantial deviations from the RC-AB relaxation line. During exercise, a shift towards the left of the relaxation line, representing a decrease in AB volume subsequent to increased expiratory abdominal recruitment, was observed This was especially marked at end-expiration However, RC volume at end expiration was found to be unchanged from values recorded at quiet breathing [136]

Konno-Mead analysis, however, is limited as it does not measure diaphragmatic displacement (whose action results in combined RC and AB displacement) nor does it measure cranial displacement of the rib cage or spinal flexion/extension [133]

Incorporating the method of RC and AB volume partitioning [133] with established Pes and Pga relaxation measurements [129], the static volume-pressure characteristics of the rib cage and abdomen were evaluated [137]

Utilization of the Konno-Mead diagrams permits a non-invasive measurement of ventilation and the resulting volume measurements have been shown to be within 10% of those volumes measured with spirometry [125]

Magnetometers (for measuring RC and AB linear displacement) [138] and more recently, a respiratory inductive plethysmograph (for measuring the cross-sectional area of the RC and AB) [139] are commonly used tools to measure and characterize chest wall displacement Utilizing respiratory inductive plethysmography permits changes in the transverse direction to be measured, something not permitted in early studies utilizing linear transducers

5.2.1 Respiratory Inductive Plethysmography (RIP)

Briefly, RIP (Respitrace, Ambulatory Monitoring, Inc., White Plains, N Y.) consists of 2 coils of Teflon-insulated wire, sewn onto separate elastic bands which encircle the rib cage and the abdomen and connect to an oscillatory module Therefore, changes in the cross-sectional areas of the RC and AB alter both the self-inductance of the coils and the frequency of their oscillators, which in terms is reflected as changes in tidal volume [140,141]

Several calibration methods of RIP have been described [139,142,

143,144] A commonly used and simplistic calibration method is the isovolume manoeuvre calibration method, based upon the work of Konno and Mead **[139]** The validity of measured volumes by RIP during moderate exercise has been shown to be within 20% of those measured with spirometry, however its accuracy in monitoring end-expiratory volume is accurate only if body position remains constant (which is often impossible during exercise testing) **[139]** Satisfactory results have been obtained using Respitrace in workloads up to 1800 kpm/min, though extraneous body movement and either RC or AB wall distortion associated with much higher levels of exercise can limit its accuracy for measuring volumes Respitrace, however, does accurately monitor relative RC and AB motion during breathing and offers a simple, non-invasive method to qualitatively assess changes in chest wall displacements Qualitatively, the inference of muscle recruitment and coordination is allowed during moderate to high levels of exercise

5.3 Methods to Infer Respiratory Muscle Activity-The Analysis of Pressure Changes

Previously, only the measurement of global inspiratory or expiratory muscle activity could be quantified as the difference between the dynamic Ppl developed during breathing and the static relaxation pressure measured at the same volume In an attempt to quantify individual contributions of chest wall muscles to breathing, Goldman *et al* **[16]** investigated the relationship of Pes and Pga to RC and AB volumes They hypothesized that when the subject is upright and RC and AB muscles are relaxed, the diaphragm is the only importantly active muscle At rest, therefore, diaphragmatic contraction would result in an increase in Pga which would displace both the RC and the AB along their relaxation characteristics and the resultant fall in Ppl would act to inflate the lungs As an extension to this early study, the concept of inferring respiratory muscle action from volume-pressure partitioning was introduced **[145]** It was suggested that any observed departures from the static relaxation line when volume was plotted against pressure was a combined result of increasing muscle activity (ie intercostals/accessories) and the coordination of that activity with respiratory muscle activity in other parts of the chest wall Plotting Rib cage volume (V_{RC}) versus Ppl during breathing, observed deviations from the relaxation were said

to reflect the combined influence of the diaphragm, intercostals and accessories. Departures from the static relaxation line of V_{RC} to Pab observed during increasing ventilation was said to represent solely intercostal and accessory muscle activity

It was determined that diaphragmatic length is reflected by changes in abdominal volume **[146]** It was observed that during increasing levels of exercise, end-inspiratory diaphragmatic length did not change however at end-expiration, the diaphragm was lengthened (inferred by observed decreases in abdominal volume) This led to the proposal that active expiratory abdominal muscle contraction appears to have an important inspiratory role This active expiratory abdominal activity results in a lengthening of the diaphragm to a more optimal length **[7]**, subsequently decreasing the load placed upon the diaphragm by the subsequent inspiration **[146]** In conclusion, it was believed that increasing activity of both RC and AB muscles observed during exercise functioned to optimize diaphragmatic function **[145]** During exercise, the observation was made that during inspiration, no change in Pab sometimes occurred It was thus concluded that the diaphragm was no longer functioning to displace the chest wall but rather the RC and AB muscles, working in series with the diaphragm, had taken over that role and the diaphragm's sole function was to inflate the lungs ($\Delta Pdi=-\Delta Ppl$) **[145]**

In contrast, Macklem *et al* proposed that the intercostal/accessory muscles and diaphragm act more in parallel, and that the diaphragm was capable of contracting quasi-isometrically, acting as a fixator to prevent the transmission of Ppl to the AB, hence not performing any external work **[147]** Therefore, if the AB muscles are relaxed and $\Delta Pab = 0$, these investigators deduced that $-\Delta Ppl$ was achieved by a combination of contracting the intercostal/accessory muscles and by quasi-isometrically contracting the diaphragm where in contrast to earlier studies where they concluded that the intercostal/accessory muscles were solely responsible for all work required to inflate the lung **[147]**

5.3 1 The Macklem Diagram

The Macklem diagram was thus developed as another attempt to infer inspiratory muscle activity **[fig 5 2]** The Macklem diagram plots Pel (or esophageal pressure (Pes)) measured via an esophageal balloon versus Pab (measured via a gastric balloon) and

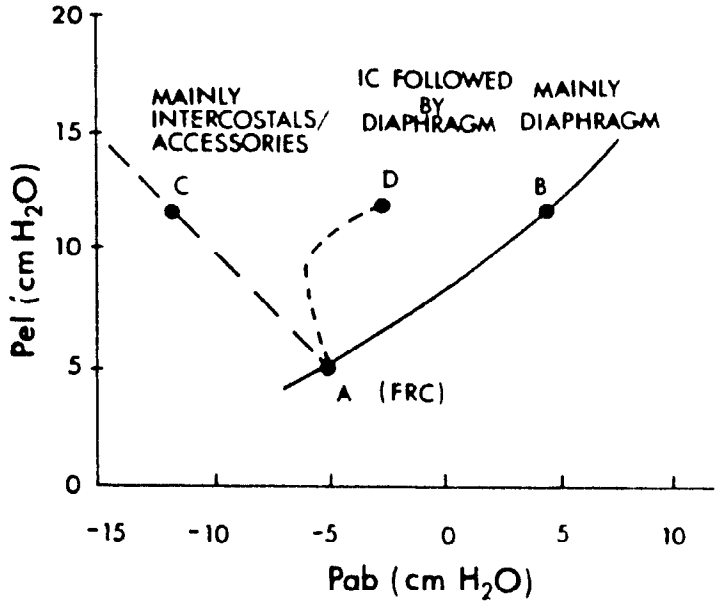


Figure 5.2 Macklem diagram **[147]**.

provides a means of inferring the pattern of recruitment of muscles without having to measure volume or chest wall displacement During quiet breathing, similar results were found by previous investigators **[16]**, whereby the diaphragm appeared to be the major muscle contracting and the Ppl-Pab relationship lies along the relaxation line (line AB) Displacement off this relaxation line infers inspiratory muscle recruitment When only the intercostal/accessory muscles are active, Ppl decreases and Pab decreases by the same amount (Ppl is transmitted through a passive diaphragm), resulting in rib cage expansion and a paradoxical inward movement of the relaxed abdominal wall (line AC) Intermediate patterns are said to represent the combined action of intercostals and the diaphragm (line AD) **[125,147]**

The idea of a quasi-isometric diaphragmatic contraction has now been rejected. It now appears that mechanically the diaphragm and rib-cage muscles are linked both in parallel and in series as they act together upon inspiration **[148]**. If the rib cage expands and the diaphragm is solely acting as a fixator, abdominal pressure should decrease since the RC would act to expand that part of the abdomen contained within the diaphragm, thus resulting in a decrease in Pab unless abdominal muscle tone increased or some diaphragmatic contraction occurred **[149]**

Although the quantification of the contribution to breathing of individual muscles can not be achieved through the use of Macklem diagrams (ie the abdominal wall is never totally relaxed during exercise), the Macklem diagram does permit the qualitative inference of respiratory muscle recruitment Pdi iso-lines, whereby Pdi = 0, can be construed and thus permitting the calculation of the total diaphragmatic contribution in terms of pleural and abdominal pressure changes from the x-y coordinates of the Ppl-Pab plot **[125]** Combining both the relative motion diagrams introduced by Konno and Mead and the Pes-Pga analysis achieved through the use of Macklem diagrams provides the investigator with a simplified method of qualifying respiratory muscle activity

CHAPTER 6 RESPIRATORY PSYCHOPHYSICS

6.1 Historical Development

The exploration and elucidation of the subjective sensory process has largely been addressed through the science of psychophysics Unlike objective sensory physiology, where one is able to measure both the strength of the stimulus and the amplitude of the response through either physical or chemical means, subjective sensory studies utilize unique subjective measurement systems **[150]**

In 1846, Weber reported that the "just noticeable difference" (JND) in intensity between two stimuli is a constant fraction of the intensity of the first stimulus (Weber's Law) **[151]** In 1859, G T Fechner defined psychophysics as an exact theory of the relation of body and mind **[152]** and based on Weber's findings, developed a law stating that sensation intensity grows as a function of the logarithm of the stimulus (Fechner's Law) **[153]**

S S Steven's modified these early assumptions of Fechner and reported that the psychological magnitude of a given sensation is a power function of the physical magnitude of the stimuli, (Steven's Power Law), **[153]**,

$$\psi = k\Phi^{n} \qquad (1)$$

whereby ψ = the psychological magnitude of the perceived sensation
Φ = the physical magnitude of the stimulus
k = a constant
n = the associated exponent

The value of n can be obtained by performing a logarithmic transform of the relationship, $\log \Psi = \log K + n \log \Phi$ Therefore, n is the slope of the best-fitting regression line between stimulus magnitude and stimulus intensity, and its value has been used to quantify subjects' responses or perceptual sensitivities to a variety of added stimuli Perceived magnitude may rise faster than stimulus magnitude, $n>1$, it may rise at the same rate, $n=1$, or it may rise slower, $n<1$ **[154]** Most psychophysical relations may be described by Steven's Power Law, with exponents of n ranging from 0 3 to 3 The value of n has been utilized to describe the relationship between sensory magnitudes and to

evaluate differences in sensory perception between subjects and under different experimental conditions

A large range of subjective sensations, examined under many stimuli and by varying methodologies have been quantified through the use of Steven's Power Law [153,155,156] These studies have provided the basis for the direct scaling methods used in studies of respiratory sensations.

6.2 Scaling Methods

A number of potential scales exist, each demonstrating intrinsicly different mathematical and statistical properties [157] There are two main ways one can construct a sensation or response scale, indirectly and directly.

6.2.1 Indirect Scaling

The first approach is "indirect" scaling, whereby the subject perceives one stimulus from another This approach applies Weber's JND concept and its use has largely been associated with qualifying, rather than quantifying perceptions [156,158]

6 2 2 Direct Scaling

The concept of direct scaling in psychophysics has largely been contributed through the works of S S Stevens, based upon his Power Law relationship In direct scaling tasks, observers make quantitative judgements of sensory magnitude [153,159,160]. There are two types of direct scaling, ratio scaling and category scaling

6.2.2 1 Ratio Scaling

A ratio scale is one that possess a unique zero. Subjects are asked to rate their perceived sensation based on a ratio relationship For example, the subject may use any number, including fractions, to assess sensation The subject is to'd to focus on ratio relationships among stimulus intensities If one stimulus appears five times as intense as another, this judgement could be represented by the numbers 1 and 5 or 5 and 25 respectively [159]

6.2.2.1.1 Magnitude Estimation

Magnitude estimation, developed by Stevens **[161]**, is a commonly used ratio technique to assess perceived stimulus intensities Subjects are asked to give a direct numerical estimation of their subjective sensation for each of several stimulus levels, either with reference to a given standard stimulus or with no previously given standard The majority of magnitude estimation studies employ the latter, termed open magnitude scaling Studies have demonstrated the validity of Steven's power law for a number of perceived sensations scaled through magnitude estimation **[153,156]**

6 2.2.1.2 Magnitude Production

This technique involves the experimenter presenting numbers one at a time in a random order, and the subject is asked to adjust the stimulus to match the given numerical value **[161]**

6.2.2.1.3 Cross-modality Matching

Subjects are asked to manipulate the intensity of a stimulus in one modality, e g loudness, to match the perceived intensity of the magnitude of the stimulus of a different modality, e g light intensity **[159]**

One major drawback of ratio scaling is in its ability to quantitatively permit inter-subject comparison and evaluation

6.2.2.2 Category Scaling

The subject is asked to rate their perceived sensation on a provided scale, which is limited by an interval range and type of numbers (ie subject is not permitted to fractionize) A true zero does not exist Though Stevens has cautioned on the use of such category scales to quantify perceived sensations **[152]**, recent investigators have returned to modified category scales for investigating perceived sensations in the clinical setting as they permit inter-subject comparisons

6 2 2 3 Visual Analogue Scale (VAS)

The visual analogue scale (VAS) is one type of a ratio, interval scale which has been utilized in the quantification of a variety of sensations **[162,163,164]** The VAS consists of a line, usually 100 mm in length, which represents the full range of severity of the investigated sensation The line may be oriented either horizontally **[162]**, or vertically **[164]** In studies of dyspnea, the bottom of the scale is described by a phrase such as "no breathlessness" while the top of the scale is tagged by the phrase "greatest breathlessness" or "maximum imaginable breathlessness" **[164,165]** Subjects are asked to mark on the scale their level of the sensation under investigation at given intervals of time and the distance (ie in millimeters) from the bottom of the scale to the marked level of sensation is quantified Subjects freely set their own interval size, consequently, inter-individual comparisons are still problematic **[166]**

6.2.2.4 Category-Ratio Scaling-The BORG Scale

One major drawback with previously mentioned ratio-scaling methods is that they do not provide any direct "levels" for inter-individual comparisons However, utilizing a ratio scale does permit mathematical calculations (ie using Steven's Power Law) and within subject comparisons of perceptual sensitivity **[167]**

Owing to his studies of perceived exertion, Borg's Rating of Perceived Exertion (RPE) scale was devised to create a linear relationship between heart rate and exercise intensity for work on a cycle ergometer **[168,169]** The scale consists of both numerical values and adjective-adverbial expressions, to allow easy interpretation of the meaning of a rating value The RPE scale has been widely used in clinical studies to predict heart rate However, each individual works within their own absolute range of perception, thus inter-individual studies of perceptual sensitivity are not possible

Addressing the above issues concerning the limitations and advantages of category v ratio scales, Borg has developed a simple category scale incorporating the positive attributes of a general-ratio scale, yet the simplicity of a category scale **[170,171]**. Numbers from 0 to 10 are anchored by verbal expressions, whose simplicity and clarity are easily understood by test subjects These expressions are placed in the correct position

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

Figure 6 1 Modified Borg Scale

on a ratio scale, according to their qualitative meaning **[fig 6.1]** The resultant modified Borg Scale permits inter-subject comparisons yet has been proven to produce psychophysical functions approximating those obtained with magnitude estimation **[156,167,171,172,173]**

6 3 Respiratory Psychophysics

Progress in the study of respiratory sensations has developed slowly. Experiments relating to perceived respiratory sensation have met with methodological and conceptual difficulties, including controlling and identifying the appropriate stimulus parameters and selecting the appropriate scaling technique to quantify perceived sensations **[174]**

6.3.1 Threshold Load Detection in Normal Subjects

The first studies directly related to perceived respiratory sensation were not carried out until the early 1960's These studies focused on "indirect" measurements of respiratory sensations, specifically the JND, or Difference Threshold concept, based upon Weber's Law, $\Delta S/S = k$, which states that the change in stimulus intensity needed to produce a perceived JND (ΔS) is a constant fraction (k) of the background stimuli (S) **[160]**

Resistive loads to either inspiration, expiration or both, alter normal pressure-flow relationships and are utilized in studies of normal subjects to mimic the type of flow limitations experienced by patients with obstructive lung disease Conversely, elastic loads, which alter normal pressure-volume relationships mimic the type of volume restrictions characterized by patients with restrictive lung diseases **[159]**

Early studies of respiratory perceptions focused on the ability of man to detect a JND when small resistive and elastic loads were added at quiet breathing These investigators measured the added elastic, ΔE_{50}, or resistive load, ΔR_{50}, which elicited detection in 50% of the loading trials (threshold detection level) and confirmed that man is able to consciously detect the addition to breathing of both inspiratory elastic **[175]** and inspiratory and expiratory resistive loads **[176]**

Studies addressing resistive load threshold detection in sitting and supine positions in normals demonstrated that although the ΔR_{50} was increased in the supine position,

Weber's fraction, defined as the ratio of ΔR_{50} to the total initial background resistance, R_0 (eg of the breathing circuit and the subject's pulmonary resistance) was found to remain a constant [177] A study addressing the effects of timing, flow and lung volume on load threshold detection in normal subjects demonstrated that resistive threshold detection is subserved by the relationship between pressure and flow over the early part of inspiration and neither increasing lung volumes or increasing background loading caused a decrease in resistive load threshold detection [178] Also, other investigators demonstrated that just detectable loads were detected very early in the inspiration, close to peak flow [179,180]

6.3.2 Threshold Load Detection in Patients with Asthma and COPD

Studies on resistive load detection have been carried out in both asthmatics and patients with COPD It has been demonstrated that asthmatics demonstrate a higher than normal ΔR_{50}, yet comparable Weber fractions when compared to normal subjects Studies in patients with COPD, however, have yielded conflicting results Wiley *et al* [177] found that although the ΔR_{50} was higher in a patient with COPD the Weber fraction was similar to normal subjects However Gottfried *et al* [181,182] found that in a larger group of COPD subjects, both the resistive load detection threshold and the Weber fraction were significantly higher when compared to normals

6.3.3 Mechanisms of Threshold Load Detection

Later studies have attempted to elucidate the mechanisms underlying resistive load detection It has been demonstrated that threshold detection of added resistive loads was similar before and after vagal block, excluding the role of the vagus in resistive load detection [183] The role of the airways in resistive threshold load detection was excluded through demonstrating normal resistive threshold detection when the loads were added via a tracheostomy [184,185], normal resistive and elastic load detections following anaesthesia of both the upper and lower airways [186,187], and through the reduced sensitivity for load detection in patients with airflow obstruction [177,181,182] Resistive load threshold detection was also normal in patients with complete cervical cord

transection [185,188], with spinal anaesthesia of the thoracic cord (chest wall block) [189] and during partial curarization to weaken the respiratory muscles [190] During assisted mechanical ventilation, a deterioration in the ability to detect added resistive loads occurred [191] Based on the above, it was hypothesized that resistive load detection is in part due to afferent information generated by the inspiratory muscles and that load detection was mechanically related to the relationship between force and displacement and not merely a function of either force or displacement alone [175,176,192] and that active respiratory muscle contraction plays an essential role in the detection of added resistive loads [191,193] It has been suggested that patients suffering from COPD may have a defect in resistive-load detection (ie perception is blunted) [181,182]

6 3 4 Threshold Detection of Ventilation and Pressure

Further studies addressing ventilation and pressure threshold detections have demonstrated the ability of man to detect increases in ventilation [194], and to detect negative pressure changes at the mouth [195] Since passive ventilation and chest vibration significantly increased the pressure load detection thresholds, it was concluded that afferent information generated from actively contracting inspiratory muscles was a necessary component for pressure and ventilation threshold detection

6 3 5 Direct Scaling of Perceptions of Volume, Ventilation, Frequency and Pressure

The first attempts to apply direct scaling techniques to respiratory studies utilized open magnitude estimation and magnitude production to investigate the respiratory perceptions of ventilation, volume and pressure changes It was established that all of these sensations, regardless of the scaling technique utilized, fit Stevens' psychophysical power law model [196]

Further studies utilizing the direct scaling method of magnitude production and volume matching confirmed the power law relationship or subject's ability to perceive tidal volume, inspiratory flow, minute ventilation and respiratory frequency, with perceptual sensitivities (n) >1 [197,198,199] When comparing individual subjects, a large range of exponents exist for each measured sensation [196,197,200] although the

sensitivity of an individual to respiratory variables tends to be similar for each variable (eg subjects with a high sensitivity to Vt also tend to have a high perceptual sensitivity for pressure or ventilation scaling) [197] One group of investigators determined that the exponent for minute ventilation was significantly higher than either tidal volume or frequency, leading them to conclude that the assessment of ventilation probably provides the most significant respiratory sensation [196] while other investigators found no statistical increase in the exponent for ventilation when compared to Vt or inspiratory flow [197]

6.3.6 The Perception of Achieved Force (Tension) and Pressure

Studies on the perception of force and pressure have utilized the direct scaling method of magnitude estimation, where subjects are asked to estimate the magnitude of their perceived sensation of load elicited by either the addition of a resistive or elastic load at the mouth Loading inspiration consequently increases the respiratory effort required to maintain a given level of ventilation and causes pressures (measured as airway pressure at the mouth) generated by the inspiratory muscles to subsequently increase to match ventilatory demand, as described by the equation of motion,

$$Pmus = Vt \times E_0 + V \times R_0 \quad [201] \qquad (2)$$

whereby: Pmus = pressure developed by the inspiratory muscles
Vt = tidal volume
E_0 = elastance
V = flow
R_0 = resistance

It has been demonstrated that the perceived magnitude of added loads to breathing in normal subjects and patients with COPD grows as a power function of the added load [181,202] Within subjects, the rate at which the sensory magnitude increased was highly correlated during both elastic and resistive loading, but again, great inter-subject variability existed This indicates that some individuals were more "sensitive" perceiving the added loads than others [202]

It was also demonstrated that fixing flow rates during resistive loading and volumes during elastic loading caused the perceived magnitude of the loads to increase It was concluded that either the actual tidal volume and flow rates adopted or factors related to

them, such as muscular effort, were important attributes of the sensation elicited by loading breathing [202]

Further investigation of load sensation in normals confirms that the perceived magnitudes of added resistive and elastic loads at rest and during increased ventilatory drive (by exercise, CO2-stimulated breathing and hypoxia) is a direct function of peak airway pressure during inspiration (an index of changes in respiratory muscle tension) generated to overcome the load and an indirect function of the actual added resistance or elastance or combination of both (at comparable inspiratory pressures) [203,204,205] Also, it has been observed that perceptual magnitude of added resistive and elastic loads increases as the inspiratory duration of pressure development (during loading and static inspiratory manoeuvres) increases [204,206]

6 3 7 Magnitude Estimation of Loads in COPD Patients

A study examining the perceptual sensitivity of a group of COPD patients found that the exponent of magnitude estimation to added resistive loads was significantly lower when compared to normals and that adjustment for background airway resistance did not improve the measured sensitivity [182] A group of asthmatic patients, however, demonstrated similar sensitivity when compared to normal subjects Patients suffering from COPD have long term, intrinsic resistive loading of their respiratory systems, and consequently are already experiencing chronic background resistive loading In contrast, asthmatic patients only experience periodic increases in background resistive loading during acute exacerbations of the disease Therefore, it was hypothesized that COPD patients have developed blunted perception to increasing resistive loads [182] and that the mechanism responsible for load detection can be altered by the loading history of the respiratory muscles [207] Moreover, COPD patients tend to be older and it has been demonstrated that age does play an important role in the perceived sensation of added loads Perceptual sensitivity of added elastic and resistive loads is less in older subjects, when compared to younger normals [208,209,210] In contrast, the perceived sensation of respiratory muscle force during static inspiratory pressure manoeuvres does not differ between ages [211]

The early study of the perceptual sensitivity of COPD patients to resistive loading [182] did not take into account age, however, later studies using COPD patients and age-matched normals have shown conflicting results. One study showed that when COPD subjects are compared to age-matched normals, the perceived magnitude of added loads were similar [210], whereas another study demonstrated that even after correction for inspiratory durations, COPD subjects demonstrated lower sensitivity to added elastic and resistive loads when compared to age-matched normals [212].

6.3.8 Mechanisms of the Perceived Magnitude of Volume and Added Loads

It has been suggested that the sensation of volume is mediated by afferent information generated by receptors affected by active respiratory muscle contraction [197]. Many factors influence the sensory magnitude of added loads to breathing, however, the pattern of breathing adopted in overcoming the load (ie. the combination of inspiratory flow and time with resistive loading, and the combination of tidal volume and time with elastic loading) [204,210] and the age of the subjects [208,209,210] appear to play roles. These authors concluded that the blunted perceptions to added loads observed in COPD patients was due to their adopted breathing patterns of low inspiratory flow rates and shorter inspiratory duration times, compounded by their increased age. Both of these mechanisms act to lower the perceived sensation of their disease-added intrinsic resistive load [210]. This conclusion is disputed by those investigators who demonstrated that neither age nor reduced inspiratory durations could explain the abnormalities in load sensations observed in COPD patients [212].

During a magnitude production study of respiratory force at varying lung volumes, it was determined that the sensation of respiratory muscle force is based primarily on signals related to tension developed by the actively contracting muscles [203]. Resistive and elastic loading studies in low cervical cord transections demonstrated that their sense of loading was impaired, supporting the hypothesis that the sense of force is in part due to afferent signals (tension) from rib cage muscle receptors during active breathing [213]. However, it is believed that under conditions of extreme inspiratory muscle fatigue or weakness, whereby afferent information from the muscles is greatly impaired, subjects

associate the perception of force with the sensation of innervation associated with the outgoing motor command to the muscles from the central nervous system [190,214]

6.3 9 Effects of Background Loading on Magnitude Estimation of Resistive Loads

It has been shown in normal subjects that the sensitivity of applied resistive loads increased when background resistive or elastic loads were applied, measured by cross modality matching and magnitude estimation However, adjustment of the magnitude of the loading stimulus, by subtracting either the actual added background resistance or the increase in pressure necessary to overcome the background load, resulted in similar responses to loading as with non-background loaded conditions [215] Other investigators also observed that the perceptual performance of magnitude estimation of resistive loads was not altered by background loading in normal subjects [216] It was demonstrated, however, that short term exposure to extreme background loads in normal subjects resulted in adaptation of the mechanisms subserving load perception The subject's response (n) was not changed but the actual intensities of the added loads were perceived to be less than during non-background loaded conditions [207]

6.3 10 Perception of Force Versus Perception of Effort

There is debate as to whether the perceived magnitude of added loads is related to the sense of force/tension or to the sense of effort required to overcome the load

It has been shown that subjects are able to distinguish between the sense of force and sense of effort, indicating two distinct sensory mechanisms A subject's sense of force/tension is their perceived magnitude of the actual amount of force/tension being developed by the muscles to overcome a given load Their sense of effort, meanwhile, is their measurement of how much actual effort or work they are exerting to overcome that same load It also appears that when subjects are asked to rate perceived magnitude of load, they are actually rating their perceived sense of force and not effort This is supported by studies whereby the perceived magnitude of an added load or of a static pressure manoeuvre is not increased as lung volumes are increased [203,206] At higher lung volumes, more motor output command to the muscles is necessary to achieve the required

tension (since the muscles are shortened) In fact, in one of the above studies, the subjects stated that the effort required to produce the target pressures was markedly increased at increased lung volumes [206] Also, subjects suffering from inspiratory muscle fatigue have demonstrated the ability to clearly distinguish and estimate the perceived magnitude of tension and effort during static maximum inspiratory pressure (MIP) manoeuvres The perceived tension decreased with fatigue whereas effort increased in studies where the inspiratory muscles were weakened by fatigue [214] Killian *et al* [217] demonstrated, utilizing open magnitude estimation and the Borg scale (category scale), that the sense of effort and sense of tension both increase with increasing inspiratory pressure generation, however only the sense of effort was increased with increasing lung volumes

These authors also addressed the sensation of dyspnea or breathlessness They found that breathlessness, like effort sensation, was increased with increasing pressure generation at higher lung volumes This study was important in the development of the concept that dyspnea is related to the conscious sensation of the outgoing motor command to the inspiratory muscles and is mediated by the same mechanism which subserves effort sensation.

CHAPTER 7 DYSPNEA

Dyspnea is a medical term used to characterize the non-specific complaint of difficult or laboured breathing It is often the primary symptom of patients suffering from respiratory disease Although a symptom, dyspnea is also a subjective sensation, and many authors have used such terms as breathlessness and shortness of breath synonymously [159,218] One of the major problems with addressing the issue of a specific definition for dyspnea is that the exact stimulus for this sensation is unknown [219] Numerous authors have proposed definitions of dyspnea, but as of yet, no clear and unanimously accepted definition exists [Table 7.1]

Table 7 1 Definitions of Dyspnea Proposed by Various Authors

1 The consciousness of the necessity for increased respiratory effort [220,221]
2 A sensation of laboured or difficult breathing [222,223]
3 Pathological breathlessness [224]
4 Undue awareness of breathing or awareness of difficulty in breathing [218].
5 Conscious awareness of outgoing motor command to the inspiratory muscles [225].
6 Quantitative non-threshold sensation of the motor effort required of the respiratory muscles [201]
7 Increased effort in act of breathing [226]
8 Inspiratory effort sensation [217]

7.1 Methods Used to Quantify Dyspnea

Clinical dyspnea ratings (ie the Baseline Dyspnea Index, the Transition Dyspnea Index [227], the Medical Research Council Scale [228]) are indices often used in the hospital setting to evaluate the functional impact of dyspnea on patients' activities of daily living However, the contribution of both emotional and psychological factors play a major role in a patient's subjective response [229] Psychophysical tests provide different results in dyspnea perception when compared to clinical dyspnea ratings in the same subject group [230] Clinical dyspnea ratings are mainly used as a monitoring tool of the impact of chronic dyspnea on patient's daily life, whereas psychophysical testing

addresses the perception of acute dyspnea, induced in the laboratory setting

In psychophysical testing, the intensity of dyspnea is directly related to measures of ventilation, respiratory muscle contractility and force output, and cardiovascular performance, therefore providing an objective measure of the contributing physiological mechanisms involved in the perception of dyspnea **[230,231]**

7.2 Psychophysical Testing and Dyspnea

Open magnitude scaling **[165]**, the Borg scale **[166,232]** and the VAS **[165,166,232]** have all been used to quantify the perception of dyspnea during a variety of methods of ventilatory stimulation Ventilatory stimulation has been achieved through hypercapnia **[165]**, hypoxia **[165]**, added resistive loads to breathing **[233]** and exercise **[165,166,232,233]**

7.2.1 Dyspnea During Hypercapnic and Hypoxic Ventilatory Stimulation

It has been hypothesized that afferent signals arising from both central and peripheral chemoreceptors in response to changes in the PO_2, PCO_2 or hydrogen ions in the blood may be responsible for the perception of breathlessness The chemical stimulation of ventilation through hypercapnia or hypoxia has been shown to induce breathlessness **[222,234,235]** However, it has been concluded that with hypercapnic stimulation, increased breathlessness cannot result from the straightforward perception of afferent information arising from arterial chemoreceptors Given that a clear and reproducible relationship of dyspnea to increasing ventilation due to chemical stimuli has been demonstrated **[236,237]**, it has been suggested that dyspnea perception is related to the effective ventilatory response **[233,238]**

The effects of hypoxia on breathlessness remains more controversial Some investigators have observed that the reduction in breathlessness produced by preventing exercise desaturation in COPD patients 1 was in proportion to the reduction in ventilation **[239]**, 2 could not be explained solely by the accompanying decrease in ventilation **[240]**; and in contrast, 3 that an increase in breathlessness was observed in relation to ventilation when breathing supplemental oxygen **[241]**.

7 2.2 The Role of Vagal Afferents in the Perception of Breathlessness

Pulmonary afferent neural information has been hypothesized to play a direct role in the mediation of dyspnea [222,242] This has been based on studies whereby vagal blockade has led to a reduction in shortness of breath in patients with pulmonary disease [243,244] However, recent studies in patients with heart-lung transplantation (pulmonary denervation) supports the hypothesis that vagal mechanisms contribute to dyspnea only indirectly, through the modulation of the pattern of ventilation, thus influencing the pattern of respiratory muscle activation [222,245]

7.2.3 Exercise Testing and Dyspnea

Exercise offers several advantages in the study of dyspnea when compared to other artificial means of stimulating ventilation (ie hypercapnia and hypoxia) It directly simulates demands placed upon the inspiratory muscles (increasing force and effort requirements) which an individual is faced with during daily physical activities [219,246]

7.2.3.1 Dyspnea as a Function of Workload

During progressive exercise testing, normal subjects exhibit an absence of breathlessness at very low levels of work (measured in kpm/min or watts). Dyspnea, however, increases in a curvilinear fashion as exercise progresses, demonstrating a rapid increase and reaching values between 7 and 10 as rated on the Borg scale near maximal exercise [233,247] The addition of resistive inspiratory loads in normal subjects increases the perceived level of dyspnea for a given level of work and with increasing loading, exercise capacity is diminished [233]

In a group of cardiorespiratory patients during a progressive exercise test, breathlessness has also been shown to systematically increase with increasing levels of work, with dyspnea ratings on the Borg scale of severe (5) to maximal (10) at maximum exercise However, a wide inter-subject variation was shown to exist in the rating of dyspnea for any given level of work Some patients presented with a similar response to exercise as normals, with no dyspnea perceived at rest or for low levels of work However others presented with dyspnea at rest and more rapid increases in perceived dyspnea with

increasing work It was observed that a wide variability still existed when dyspnea was plotted as a function of workload, normalized for the predicted maximum **[248]**

7.2.3.2 Dyspnea as a Function of Ventilation

Numerous authors have demonstrated that the intensity of dyspnea progressively increases with increasing levels of minute ventilation ($\dot{V}_E$) during progressive exercise, in both normal and COPD subjects **[165,240,249,250,251,252,253,254]** COPD subjects, however, experience higher degrees of dyspnea for a given level of $\dot{V}_E$ when compared to normal subjects

The rationale for using $\dot{V}_E$ is that it represents the total output from the respiratory system and correlates significantly with ratings of breathlessness during exercise **[219]** Using both the VAS and Borg scale, the intensity of breathlessness at comparable levels of ventilation has been shown to be quite reproducible within a subject upon repeat testing **[165,232]** However, inter-subject variation exists in the perceived dyspnea for any given level of absolute ventilation, both in normal **[222,245]** and COPD subjects **[248]** It is believed that it is not simply the level of ventilation, though, which determines the intensity of the dyspnea perceived, but rather how much of the total ventilatory capacity is being utilized This idea has led investigators to normalize $\dot{V}_E$ by the maximum voluntary ventilation (MVV) Investigators have utilized both the true measured MVV, calculated through pulmonary function testing **[255]**, or a predicted value for the subject's MVV, based upon the equation

$$MVV = FEV_1 \times 35 \quad \textbf{[245,248,256,257]} \qquad (1)$$

A recent study, however, demonstrated quite a large variability in the MVV/FEV_1 ratio between subjects (both normals and patients) and demonstrated that

$$MVV = FEV_1 \times 42 \quad \textbf{[258]} \qquad (2)$$

represents a more average value for predicting the MVV across a wide range of subjects There have been conflicting results when dyspnea has been expressed as a function of $\dot{V}_E/MVV$ Some authors demonstrated that no difference existed between normal and COPD subjects' perceived difficulty of breathing when $\dot{V}_E$ was expressed as a fraction of the MVV **[203]** Others have shown that in both normal subjects, heart lung recipients

[245], and in a group of cardiorespiratory patients [248], a wide inter-subject variation existed in the dyspnea response to VE/MVV

Others have expanded further to suggest that breathlessness is not simply the sensing of the actual ventilation achieved but other mechanisms such as fatigue may play a role in the perception of dyspnea [259]

7 2.3 3 The Effects of External Loads on Dyspnea Perception

External resistive loads have been added to inspiration in normal subjects during progressive exercise to simulate airway obstruction Attempts to determine the effects of inspiratory loading on breathlessness have met with conflicting results Some investigators have shown that the addition of an inspiratory load during a progressive exercise test significantly increased breathlessness for a given ventilatory level [233,251,260]. It was also observed that the threshold of dyspnea perception is lowered and the slope of the response of dyspnea to VE is increased with added inspiratory loads Other investigators, however, observed no significant increase in breathlessness with the addition of low level inspiratory loads during a constant workload exercise test [261] The differences probably lie in methodology A progressive exercise test causes much higher achieved ventilation when compared to steady state exercise, and this added ventilatory stimulus may be necessary to observe the increases in dyspnea associated with the addition of inspiratory loads

It has been hypothesized that subjects' rated levels of breathlessness is also based upon their past experiences of their relationship between breathlessness and ventilation (eg. loading breathing and then removing the load) [260]

7.2.3 4 Dyspnea as a Function of Pressure Development

Mouth occlusion pressure (P_{100}) has been used as a measure of respiratory efferent activity during ventilation In order to correct for differences in maximum respiratory muscle strength and contractility, mouth pressure is expressed as a percentage of the maximum generated inspiratory airway pressure at FRC, with the airway occluded (MIP) [222] Again, results have been conflicting One study demonstrated that during progressive treadmill

exercise testing, both with and without inspiratory resistive loading, the relationship between the intensity of breathlessness and normalized occlusion pressure is the same in COPD patients as in normal subjects [222] This led to the conclusion that at a given level of respiratory motor activity, the intensity of breathlessness does not differ from normals to patients with COPD However, a more recent study demonstrated that although a direct linear relationship existed between dyspnea and $P_{0.1}$/MIP in all subjects, a wide variation in the responses (slopes of the relationships) existed [245]

Studies have also demonstrated a significant correlation between peak inspiratory mouth pressure (Pm) and perceived breathlessness, both in a group of normal subjects [217] and asthmatic patients [219]

A close relationship between dyspnea and inspiratory effort sensation (IES) is assumed [262], therefore IES and dyspnea are often used synonymously by investigators studying the mechanisms of dyspnea

Esophageal balloons can be utilized to measure esophageal pressure (Pes), which approximates pleural pressure [263] Studies in normal subjects have demonstrated a direct linear relationship between pleural pressure swings (ΔPes), ΔPes normalized as a percentage of the maximum inspiratory pressure (ΔPes/MIP) [264], and mean Pes ($\overline{Pes}$) [265] to the subjects' IES A large variability in subjects' sense of effort is observed when IES is related to the pleural pressures generated This variability was minimized when Pes was expressed as a percentage of the MIP [233]

A similar linear relationship of Pes/MIP and Pm to breathlessness, as rated on the Borg scale, has been shown in both cardiorespiratory and asthmatic subjects [248,219]

The MIP has generally been utilized as an index of respiratory muscle strength (RMS). In normal subjects, a large variation in MIP has been observed, 60 cmH20 to 300 cmH20 COPD patients also exhibit a wide variability in RMS (ie a mean value of 66 cmH20 ±20 cmH20 in a group of cardiovascular and respiratory diseased patients) [201]

Variations in RMS have been demonstrated to result in an equally large variability in IES during resistive loading in both normal and COPD subjects The sense of effort for a given pressure generated was greater for the subjects with weaker inspiratory muscles [201,246,262] The majority of all studies have utilized MIP as the normalizing value for

pleural pressure swings, however, a recent study addressed the fact that the capacity of the inspiratory muscles to generate pressures decreases with both increasing lung volumes (used as an indication of changes in respiratory muscle length) and increasing inspiratory flow rates (used as an indication of changes in the respiratory muscle velocity of contraction) [247,266,267,268,269]

This concept has led to the quantification of the capacity of the inspiratory muscle to generate pressure (P_{cap}) during exercise It was found that P_{cap} is preserved between 30 and 55% TLC, but declines by 1 7% for each 1% increase in end inspiratory lung volume above 55% TLC In addition to this volume effect, a 5% reduction in the muscles' generating capacity was observed for each litre per second increase in flow at any given lung volume Therefore, normalization of pleural pressures by MIP will underestimate the percentage of capacity being utilized by the respiratory muscles during exercise The following equation quantifies the relationship,

$$P_{cap}(\%\ max) = (MIP - 1\ 7(\%TLC)) - 5\ 0\ (l/sec)\ [247] \qquad (3)$$

These investigators found that when breathing was loaded during exercise, the sense of respiratory effort was closely correlated to the pressures generated by the respiratory muscles expressed as a percentage P_{cap} [247,270]

7 2.3.5 Dyspnea as a Function of other Physiological Parameters

A study in normal subjects undergoing exercise testing has demonstrated a significant and independent relationship of breathlessness (ψ) to peak Pes (indication of muscle tension), inspiratory flow ($\dot{V}_I$) (an indication of the velocity of inspiratory muscle shortening), the frequency of breathing (fb) and the duty cycle (T_I/T_{tot}), giving the predictive equation

$$\psi = 0\ 11(Pes) + 0.61(\dot{V}_I) + 1\ 99(T_I/T_{tot}) + 0\ 04(fb) - 2\ 60\ [233] \qquad (4)$$

Similar studies in COPD patients during exercise have also demonstrated a multi-variable relationship to breathlessness In a group of cardiorespiratory patients, the following predictive relationship for breathlessness was found:

$\psi = 3.0(PpI/MIP) + 1\ 2(\dot{V}I) + 4\ 5(V_T/VC) + 0\ 13(fb) + 5\ 6(T_I/Ttot) - 6\ 2$ (4)

Similarly, in a study of asthmatic patients, $\dot{V}_I$, V_T/FVC, fb and Pm each individually demonstrated linear relationships to subjects' levels of breathlessness as rated on the Borg scale and all variables together accounted for 63% of the variance in the rating of dyspnea [219].

7.3 The Relationship of Dyspnea to Muscle Fatigue

The role of inspiratory muscle fatigue in the development of dyspnea remains an unresolved issue. Studies have largely focused on IES during induced fatigue in normal subjects. Diaphragmatic fatigue, induced through inspiratory resistive loading, has been shown to be associated with increases in the sense of respiratory effort. However, both the intensity of the diaphragmatic contraction and changes in diaphragm activation levels were unrelated to the magnitude of the sensory perception [271]. A further study whereby diaphragmatic fatigue was induced through fatiguing contractions of the diaphragm also demonstrated that IES was independent of the transdiaphragmatic pressure (P_{di}) and could be dissociated from the development of diaphragmatic fatigue [272]. Investigators found stronger correlations between the levels of activation of both the sternomastoid and rib cage muscles and the sense of respiratory effort, leading to the conclusion that the increasing effort sensation during a diaphragmatic fatigue run was due to either the loading of the rib cage muscles or to the central perception of an overall increase in the central motor output directed towards these "accessory" muscles [271].

Other studies have induced generalized inspiratory muscle fatigue (IMF), both through continuous maximal inspiratory contraction [273] and by inspiratory threshold loading [274]. It has been demonstrated that a faster rate of increasing IES is observed with a high pressure (P_m/P_{max})-short duty cycle (T_I/T_{tot}) pattern of loaded breathing when compared to a low pressure-long duty cycle pattern, despite the maintenance of a constant pressure time index of 0.24. This led to the hypothesis that IES is related to but not a direct function of the onset and severity of IMF. IES is therefore dependent on the intensity rather than the duration of muscle contraction and may possibly occur as a result of the central perception of the subsequent increasing motor command to the fatiguing muscles.

[273,274] Varying the breathing patterns (ie predominantly rib cage, diaphragm or a combination of both) during inspiratory resistive loading in normal subjects resulted in an observed direct linear and unique relationship between ΔPes and IES, regardless of the thoracoabdominal breathing pattern adopted [265] Although imposing fatiguing diaphragmatic patterns of breathing did demonstrate a strong correlation between IES and Pes/Pesmax, IES was independent of the development of diaphragmatic fatigue [264].

It is important to note that a study addressing the perception of dyspnea associated with changing levels of ventilation demonstrated that dyspnea intensifies when the level or pattern of breathing is voluntarily changed from the spontaneously adopted level [275]. Therefore, this may compound the dyspnea which subjects perceive during studies where their breathing patterns are set or constrained

Studies of diaphragmatic fatigue and IES in COPD subjects are limited, nevertheless, it has been demonstrated that, as in normal subjects, diaphragmatic fatigue appears independent of IES [276] Also controversy exists as to whether COPD patients develop respiratory muscle fatigue during progressive exercise It has been observed that COPD subjects often develop a fatiguing pattern of inspiratory muscle contraction and/or diaphragmatic contraction during exercise [115,277,278, 279,280] In contrast, non-fatiguing patterns of both inspiratory muscles (pleural pressure-time indices (PTI) of 0 10) and the diaphragm (PTI of 0 12) have also been measured upon the cessation of exhaustive exercise [281]

Utilizing fatiguing patterns of PTI to draw conclusions regarding the relationship of IES to fatigue must be interpreted cautiously What is usually being indicated is incipient fatigue, whereby the muscles would fatigue should that pattern of contraction continue for a given length of time For example, a diaphragmatic PTI of 0 15 could be sustained for approximately 90 minutes, whereas an inspiratory muscle PTI of 0 25 could be sustained for approximately 15 minutes before signs of overt fatigue would develop [272] Also, subjects may cyclicly alternate between diaphragmatic and inspiratory muscle contraction in an attempt to limit incipient fatigue [106] It appears that normal subjects adopt a pattern of breathing which serves to optimize the sense of effort by minimizing the tension generated in the respiratory muscles [270]

Other observed signs of incipient fatigue (during observed fatigue η PTI) include a fall in the high to low ratio or centroid frequency of the EMG power spectrum, the slowing of observed inspiratory muscle relaxation, rapid shallow breathing and chest-abdomen asynchrony [282]

COPD patients often demonstrate respiratory muscle weakness and subsequent decreases in their inspiratory muscle force response after exercise (ie decreasing sternomastoid force [279]), however, one cannot assume that overt muscle fatigue has occurred They too will attempt to adopt a pattern of breathing to minimize the risk of IMF

7.4 Mechanisms of Augmentation and Relief of Dyspnea In COPD Subjects

It has been shown that in patients experiencing acute asthma attacks, dyspnea is well correlated with both hyperinflation and recruitment of the sternomastoid muscles, and that dyspnea subsides when the heightened sternomastoid activity ceases [283] Patients suffering from respiratory failure experience a loss of dyspnea when mechanically ventilated, a loss which correlates with a cessation of diaphragmatic electrical activity [284] During abdominal strapping, COPD subjects experience increased levels of dyspnea during exercise, hypothesised to be caused by a shortening of the intercostal and neck muscles and the subsequent increase in the required motor command [285] COPD patients often experience a relief in dyspnea by assuming the leaning position (supporting their upper extremities) Postural relief of dyspnea is likely due to the fact that leaning forward both improves the length-tension state and increases the efficiency of the diaphragm as well as the unloading of the rib cage accessory muscles [286] It has been observed that in a patient with bilateral diaphragm paralysis, acute dyspnea was experienced when the subject was immersed in water to the level of the abdomen Since the water now fully supported the abdominal contents, immersion prevented the passive inflationary effects of abdominal muscle contraction and eliminated inspiratory abdominal muscle relaxation This resulted in a loading of the rib cage muscles [287] All of these studies serve to emphasize the apparent significance of respiratory muscle function to the perception of dyspnea

CHAPTER 8 METHODOLOGY

It is hypothesized that high levels of ventilation should be reached at lower perceived levels of dyspnea if respiratory muscle coordination increases and the use of the diaphragm-accessory muscles is optimized. Successful athletes and/or COPD patients should therefore display high levels of ventilation at lower dyspnea. Hence we tested muscle coordination and its relationship to dyspnea in groups of athletes, normal sedentary subjects and COPD patients during high levels of exercise. Dyspnea was measured using the Borg scale. Coordination was inferred via esophageal and gastric pressure swings and chest wall-abdominal displacement during a progressive exercise test on a cycle ergometer.

The rationale underlying this hypothesis is fourfold. First, dyspnea is a quantifiable sensation which is known to be proportional to the degree of inspiratory muscle activity. Second, COPD patients do have an increased load to breathing at rest as well as at lower ventilatory levels due to the nature of their disease. Similarly, athletes also are exposed to higher respiratory loads on a regular basis when performing training which requires high levels of ventilation. Finally, sedentary normal subjects are not exposed to either of these types of loading on a regular basis.

In order to investigate this hypothesis we tested fifteen male subjects. All subjects gave informed consent prior to their participation. Four of the subjects were normal, sedentary, non-smokers and were familiar with respiratory studies. Four were defined as elite athletes, having competed in their sport internationally and who underwent daily endurance training (3 rowers, 1 cyclist). The remaining seven subjects were classified as moderate to severe COPD patients.

Prior to the study, all subjects performed standardized pulmonary function tests, using a compact Vitalograph spirometer, to determine their forced vital capacity (FVC) and forced expired volume in one second (FEV_1). The relationship of FEV_1/FVC was thus calculated. All studied patients were currently being followed at Notre Dame Hospital, Montreal, Quebec and had undergone extensive testing in the pulmonary function laboratory prior to their participation in this study. Values of Total Lung Capacity (TLC), Functional Residual Capacity (FRC) and Residual Volume (RV) were obtained from the patients'

charts. Predicted spirometric values were obtained from standardized tables, based on the subject's sex, age and height **[288,289]**

Immediately prior to exercise testing, patients were sent for an electrocardiogram, whose results were verified by a physician to ensure their suitability for exercise testing

Subjects were seated on a cycle ergometer (N V Godart, Holland #116473) where a metal bar with chest pads was adjusted and placed in front of the subject, enabling them to lean against it for improved stabilization and minimization of body movement and postural changes The handlebars of the ergometer were also stabilized to decrease extraneous body movement **[fig 8 1]**

Subjects were fitted with a headpiece to which a large two way valve was attached (Hans Rudolph Inc Kansas City, No 2700) A pneumotachograph (Fleisch no 3) was connected to the inspiratory port A rubber mouthpiece was connected to the valve and inserted into the subject's mouth The pressure gradient within the pneumotachograph was measured via a Validyne pressure transducer (±2 cmH20) For monitoring purposes, flow was electronically integrated to volume and displayed on paper utilizing a Hewlett-Packard respiratory integrator (8815A) Signal calibration was performed to minimize drift of the flow signal and the inspiratory flow was set to automatically reset to 0 at the end of each inspiration Esophageal pressure (Pes) (measured as an estimation of pleural pressure) and gastric pressure (Pga) were measured **[129,263,290]** using commercially available latex rubber balloons , 5 cm long, 0 012-0 015 cm in thickness, 3 50 cm in circumference and 1 11 cm in diameter (Medical Corporation, New Jersey), attached to 100 cm Intramedic PE 200 non-radiopaque, non-toxic polyethylene tubing with a luminal diameter of 1 40 mm, and outer diameter of 1 90 mm (Clay Adams, Division of Becton Dickinson and Company, New Jersey) The catheters were connected to separate Validyne pressure transducers (±200 cmH20 for measuring esophageal pressure changes and ±250 cmH20 for measuring gastric pressure changes) All pressure signals were demodulated and amplified by Hewlett-Packard carrier amplifiers (8805B) Both balloons were inserted via the nose into the stomach Placement of the esophageal balloon was performed by slowly retracting the balloon as the subject sniffed When the pressure changes became negative in direction as opposed to positive and a baseline resting negative pressure was observed **[291]**,

Figure 8 1 Experimental setup showing a subject seated and secured to the cycle ergometer, with mouthpiece, pneumotach, Pes and Pga balloons and Respitrace bands in place

the tubing was securely fastened at the nose via tape and a nose clip Care was also taken to place the esophageal balloon where the cardiac artifact was minimized This procedure was performed by a physician at Notre Dame Hospital who had significant experience in accurately positioning the esophageal and gastric balloons

The esophageal balloon was filled with 2 ml of air, of which 1 5 ml was then removed, leaving 0 5 ml remaining The gastric balloon was filled with 1 ml of air The compliancy of the esophageal latex balloon at a volume of 0 5 ml as an acceptable minimum unstretched volume was validated by the pulmonary function laboratory at Notre Dame Hospital Normally, the gastric balloon is thicker than the esophageal balloon, however, since the gastric balloon was not left in the stomach for a prolonged period of time, there was adequate resilience to gastric secretions and thus, the utilized balloon thickness was acceptable The polyethylene catheters were found to demonstrate a flat frequency response up to 10 Hz Frequency spectral analysis of both Pes and Pga swings demonstrated that even during maximum exercise, no frequencies of any power produced exceeded 5 5 Hz, thus validating the usage of these catheters

Rib cage (RC) and abdominal (AB) excursions were measured via respiratory inductive plethysmography (Respitrace, Ambulatory Monitoring, Inc , White Plains, N Y) The upper edge of the rib cage band was placed at the mid-axillary level, about the second to fourth intercostal area, while the upper edge of the abdominal band was placed at the level of the umbilicus above the iliac crest **[292]** Both bands were taped and secured in place Respitrace signals were amplified using two Hewlett-Packard medium gain amplifiers (8802 A) for RC and AB signals respectively

All signals were displayed on a Hewlett-Packard 8 channel paper recorder (7758A) and recorded on analog magnetic tape (Hewlett-Packard instrumentation recorder 3968A) for future playback and computer analysis

A four lead electrocardiogram was also utilized, connected to an oscilloscope for the monitoring of cardiac electrical activity throughout the exercise test for safety reasons and an attending physician was present throughout the study

All channels were calibrated prior to beginning the exercise test and calibrated again at the end of the session, to minimize error and assure accuracy Once the setup was

completed, subjects were asked to perform a static maximum inspiratory pressure manoeuvre (MIP) at functional residual capacity (FRC) with airways closed, while in the se ed position on the ergometer This was repeated until consistent results were obtained

Subjects were also asked to perform a static maximum transdiaphragmatic pressure manoeuvre (Pdi_{max}), also at functional residual capacity with airways closed while seated The Pdi_{max} manoeuvre was performed as follows Subjects were first asked to maximally activate their diaphragm-abdomen by asking them to "bear down as for defecation" While maintaining this maximal expulsive effort, subjects were asked to perform a maximal inspiratory (Mueller) manoeuvre where they vigorously attempted to suck in air against a closed glottis **[293]** This manoeuvre was repeated until consistent results were obtained

The Respitrace was calibrated by having the subjects perform isovolume manoeuvres **[133]**

Subjects were informed that during the exercise test, they would be asked periodically to rate "how short of breath" they were on a modified Borg Scale **[171]**, which was clearly displayed in front of them They were informed that they could choose any number, or fraction thereof and to exclude any other sensations (ie limb pain) they might be experiencing when they made their rating

A period of quiet breathing was monitored until all signals had reached a steady state Subjects then began a progressive exercise test, with 20 watt increments in workload introduced every minute Subjects were requested to cycle at a constant rate of 40 RPM At the end of each minute, prior to the next increase in workload, heart rate was recorded and subjects were asked to rate their level of breathlessness

Subjects were encouraged to continue cycling until exhaustion After cessation of the exercise test, subjects were asked to continue to cycle at their own pace, and at the end of each minute, their level of breathlessness and pulse rate were again monitored The test ended when both of these values reached their pre-exercise resting levels Although the data recorded post-exercise was not included in the data analysis, the subjects performed this "cool down" segment for safety reasons

8.1 Computer Analysis

The signals of the five recorded channels (Flow, Pes, Pga, RC, AB) were digitally sampled to a personal computer (IBM 386) using a software, acquisition package (Labdat Version 2.0), through an A\D Board (National Instruments No MC-MIO-16) and stored for future off-line analysis The patients' data was sampled at 100 Hz, whereas the normals' and athletes' data were sampled at 200 Hz, given the extremely rapid breathing responses observed during maximum exercise Inspiratory flow (V) was electrically integrated to volume using a software respiratory analysis program (Resp, written by Doug Wight, Notre Dame Hospital, 1991) and the transdiaphragmatic pressure (Pdi) signal was calculated by the following equation

$$Pdi = Pga - Pes \quad \textbf{[129]} \qquad (1)$$

A breath by breath analysis was performed on five breaths of quiet breathing prior to exercise, and on the last five breaths of each consecutive minute of exercise at a given workload for each subject

The following ventilation parameters were calculated for each breath, utilizing 0 flow as the beginning of Ti and the end of inspiratory flow as the end of Ti **[Figure 8.2a]** inspiratory tidal volume (Vt), inspiratory time (Ti), expiratory time (Te), total time of the breath (T_{TOT}), the ventilatory duty cycle (Ti/T_{TOT}), frequency of breathing in one minute (fb) by the following equation.

$$fb = 60 / T_{TOT} \qquad (2)$$

Also minute ventilation (VE) whereby

$$VE = fb \times Vt \qquad (3)$$

and minute ventilation normalized for lung size and disease obstruction (VE/FVC) were calculated. Each subject's individual maximum voluntary ventilation (MVV) was predicted utilizing the equation

$$MVV = FEV_1 \times 42 \quad \textbf{[258]} \qquad (4)$$

permitting the estimation of the percentage of the subject's maximum ventilatory capacity that was being utilized during exercise (VE/MVV)

Since the decline of Pes often precedes flow (pressure events can occur prior to the observation of a mechanical event), the following pressure parameters were separately

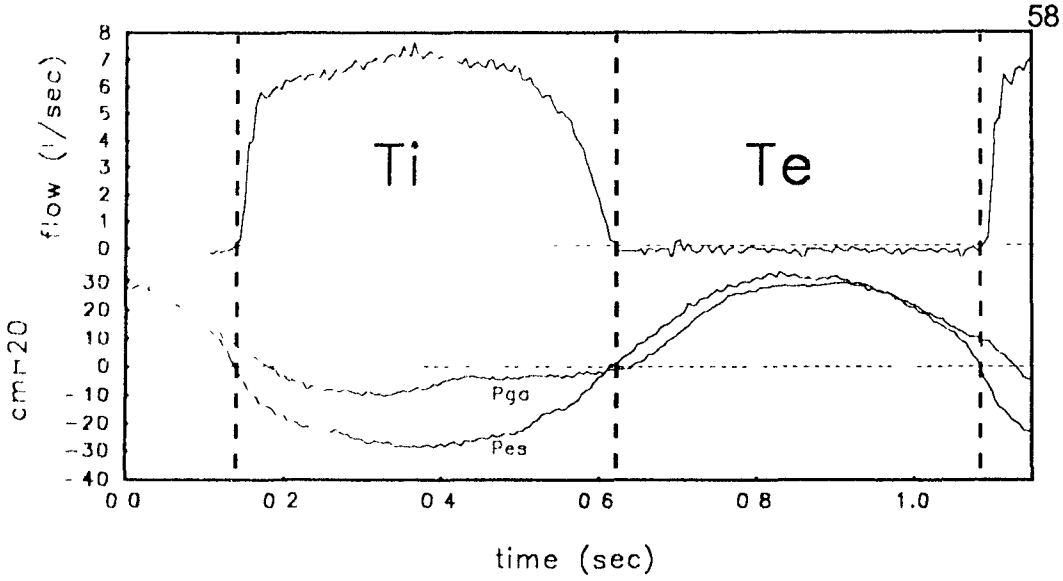


Figure 8 2 a Measured Ti and Te utilizing the onset of inspiratory flow as the beginning of Ti. This method was utilized to calculate the Ti/Ttot (duty cycle) of ventilation.

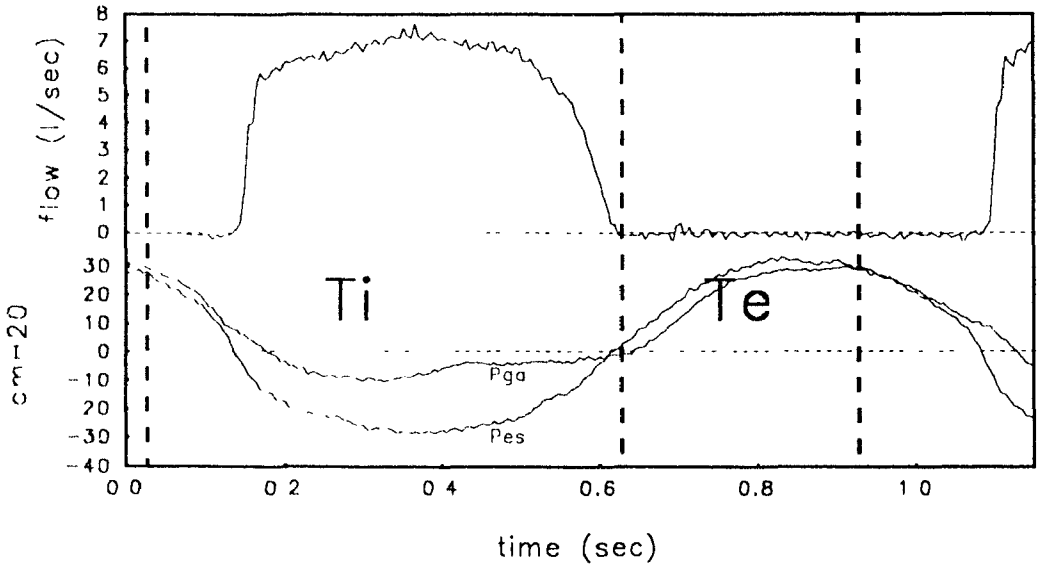


Figure 8.2.b Measured Ti and Te, utilizing the onset of the negative pleural pressure swing as the beginning of Ti. This method was utilized to calculate the pressure Ti/Ttot (duty cycle).

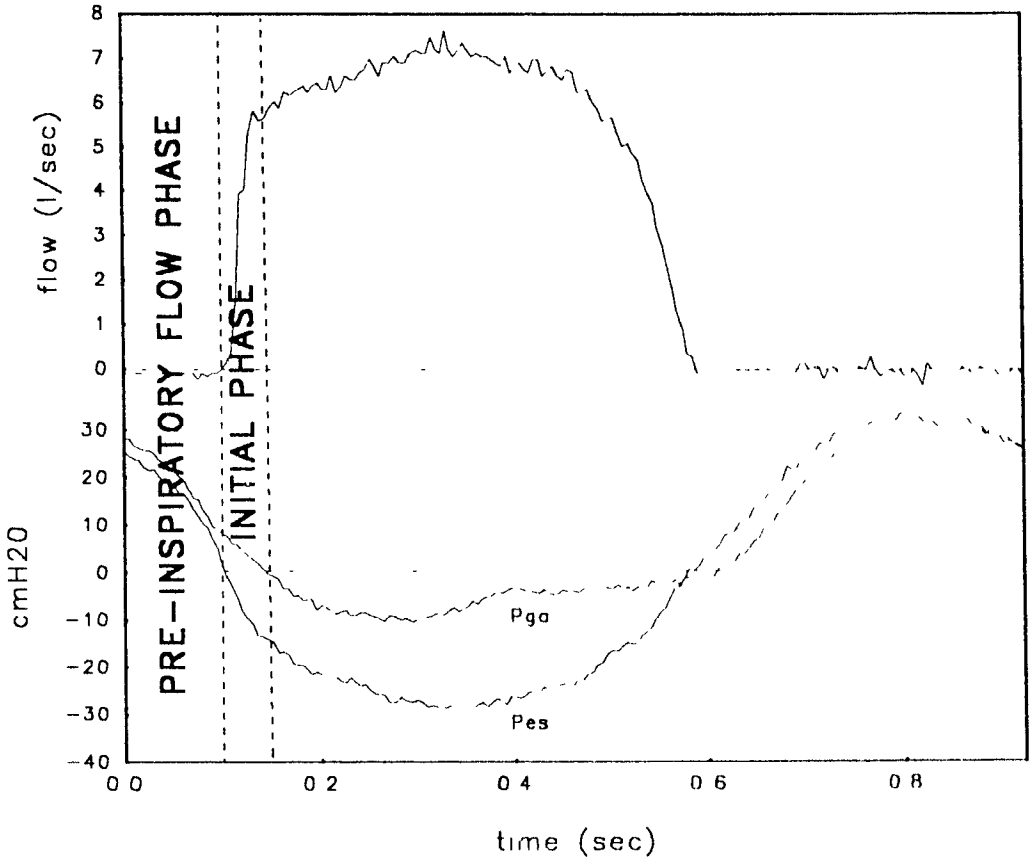


Figure 8.3 The pre-inspiratory flow phase, defined as the time from the onset of the negative pleural pressure swing to the onset of inspiratory flow, and the initial phase of pressure generation, defined as the time from the onset of inspiratory flow to the peak flow acceleration, are illustrated

measured, utilizing the onset of the negative Pes swing (when simultaneous changes in Pga were observed) as the onset of the Ti related to pressure and the end of Ti as the point where inspiratory flow ends **[Figure 8.2b]** peak to peak pleural pressure swing (ΔPes), mean ΔPes ($\Delta\overline{Pes}$), peak to peak gastric pressure swing (ΔPga), peak to peak transdiaphragmatic pressure (ΔPdi), mean ΔPdi ($\Delta\overline{PdT}$), ΔPes normalized by maximum inspiratory pressure generated at FRC (ΔPes/MIP), ΔPes normalized by the maximum capacity pressure the inspiratory muscles are capable of producing corrected for volume and flow (ΔPes/Pcap) which assumed a progressive 10% reduction in end expiratory lung volume throughout the exercise run in both normal and athletic subjects **[247]**, mean ΔPes/Pcap ($\Delta\overline{Pes}$/Pcap), the pressure duty cycle (Ti/Ttot) and the pressure-time index of the inspiratory muscles (TT_{IM}) where

$$TT_{IM} = \Delta\overline{Pes}/Pcap \times Ti/T_{TOT} \qquad (5)$$

Also measured using this timing was $\Delta\overline{PdT}/Pdi_{max}$, and the pressure-time index of the diaphragm (TT_{di}) **[272]** where

$$TT_{di} = \Delta\overline{PdT}/Pdi_{max} \times Ti/T_{TOT} \qquad (6)$$

Two phases of the onset of each inspiratory effort were also identified The first was termed the "Pre-Inspiratory Flow" phase of inspiration and was defined as the segment of time between the onset of the negative Pes swing and the onset of inspiratory flow The second was termed the "Initial Phase", and was defined as the time between the onset of inspiratory flow and the peak of the acceleration of the inspiratory flow **[fig 8 3]**

Further parameters were thus calculated These were the rate of change of Pes with respect to time for the pre-inspiratory flow phase of inspiration ($\Delta Pes/\Delta t_{PRE}$) and the initial phase of inspiration (ΔPes/Δt) Similarly, the rate of change of Pga with respect to time for the pre-inspiratory flow phase of inspiration ($\Delta Pga/\Delta t_{PRE}$) and the initial phase of inspiration (ΔPga/Δt) were calculated

Each of the above ventilation and pressure values which were calculated for each of five breaths at the end of each minute of exercise were then averaged utilizing Sigmaplot (Jandel Scientific, Version 4 1), giving the mean ± 1 standard deviation (sd) of each measured parameter at a given workload An analysis of variance between the three groups was performed with a post Scheffe test F ratios <0 05 were considered statistically

significant For graphics purposes, signals were converted from Resp files to ASCII files, analyzed in 123 (Lotus Development Corporation, Release 2 01) and subsequently plotted utilizing Sigmaplot.

CHAPTER 9 RESULTS

The results will be divided into three main sections 1 Anthropometrics, 2 Dyspnea as a function of work, ventilation and pressure generation during progressive exercise and 3 Mechanics of breathing and coordination during progressive exercise.

9 1 Anthropometrics

Individual subject data is provided in **Table 9.1** and **Table 9.2** respectively. The mean age (± 1 standard deviation) of the patients was 62 ± 10 years, the mean age of the normals was 37 ± 5 years, while the mean age of the athletes was 22 ± 1 years

9.1 1 Pulmonary Function

All pulmonary function tests (PFT) of the normals and athletes were within a normal range when compared to predicted values The only exception was N1 who presented with an FEV_1/FVC of 65% When considering the normal predicted values for a male, aged 37 and 175 cm in height **[289]**, it is found that N1's abnormally low FEV_1/FVC ratio was directly due to his extremely high measured FVC (6 15 litres versus 5 00 litres predicted). His FEV_1 was comparable to that predicted (4 0 litres)

The COPD patients presented with significant limitations in all aspects of pulmonary function Five patients were clinically and functionally diagnosed as severely obstructed and two as moderately obstructed based upon their individual FEV_1/FVC results The following values are an average of all seven COPD patients (± 1 standard deviation). FEV_1 (% predicted) 33 8 ± 15 8%, FEV_1/FVC 40 97 ± 10 93%, and RV/TLC (% predicted) 184.16 ± 35 94%

9 1.2 Respiratory Muscle Strength

The mean group Maximal Inspiratory Pressure (MIP), generated against a closed glottis at FRC of both normals and athletes were not significantly different, -130 88 ±8 29 cmH20 and -143 13 ± 19 08 cmH20, $p>0.05$. The group mean MIP value of patients was significantly reduced (-63 94 ± 18 81 cmH20, $p<0.05$) when compared to both the athletic

SUBJECT	AGE (yrs)	HT (cm)	WT (kg)	FEV_1 (l)	FEV_1 (%Pred)	FVC (l)	FEV_1/FVC (%)	RV/TLC (%Pred)	MIP (cmH20)	Pdi_{max} (cmH20)
P1	49	175	91	2 30	55 40	4 27	54 00	144 17	-50 70	86 53
P2	49	167	54	0 65	17 30	2 40	27 00	252 31	-40 00	62 46
P3	73	167	58	1 07	42 30	2 51	42 60	172 19	-50 00	60 00
P4	67	177	84	1 02	26 60	2 60	39 40	167 45	-65 00	80 19
P5	70	160	71	0 72	24 90	1 83	39 50	190 19	-83 16	99 41
P6	69	178	81	1 58	51 90	2 89	55 00	158 69	-92 30	121 8
P7	61	165	77	0 52	18 50	1 80	28 89	204 13	-66 43	68 00
Mean ±sd	62 ±10	170 ±7	73 ±13	1 12 ±0 63	33 80 ±15 80	2 61 ±0 83	40 97 ±10 93	184 16 ±35 94	-63 94 ±18 81	82 62 ±22 25

Table 9.1 Patient Data

SUBJECT	AGE (yrs)	HT (cm)	WT (kg)	FEV_1 (l)	FVC (l)	FEV1/FVC (%)	MIP (cmH20)	Pdi_{max} (cmH20)
N1	37	175	72	4 00	6 15	65 00	-138 00	194 00
N2	38	181	76	4 19	5 27	79 00	-138 00	204 00
N3	43	176	72	4 38	5 34	82 00	-125 13	166 32
N4	30	170	63	3 97	4 57	86 80	-122 40	157 85
Mean ±sd	37 ±5	176 ±5	71 ±6	4 14 ±0 19	5 ?? ±0 65	78 30 ±9 40	-130 88 ±8 29	180 54 ±21 97
A1	21	188	86	5 95	7 05	84 40	-120 00	210 00
A2	21	190	85	5 46	6 70	81 50	-135 00	169 64
A3	23	176	75	4 90	5 70	86 00	-160 00	178 60
A4	23	173	70	4 76	5 71	83 40	-157 50	195 40
Mean ±sd	22 ±1	182 ±9	79 ±8	5 27 ±0 55	6 29 ±0 69	83 80 ±1 90	-143 13 ±19 08	188 41 ±17 92

Table 9.2 Normal Sedentary Subjects (N) and Athletes (A)

and normal groups. Mean group Maximal Transdiaphragmatic Pressures (Pdi_{max}) of both normals and athletes also were not significantly different, 188 41 ± 17 92 cmH20 and 180 54 ±21.97 cmH20, whereas the mean Pdi_{max} value of the patient group was significantly reduced, 82 62 ±22 24 cmH20, p<0 05 The range of Pdi_{max} values within the patient group was 60 00 to 121.8 cmH20

9.2 The Relationship of Dyspnea to Work

9.2.1 Dyspnea as a Function of Workload (Watts)

The athletic group reached a statistically higher mean level of absolute work (measured in watts) at maximum exercise, range 320-400 watts, than both the normal group, range 200-320 watts and patient group, range 40-120 watts, p<0 05 Since the workload was increased at one minute intervals in all subjects, athletes also demonstrated much longer endurance time, range 17 to 21 minutes, when compared to the normal subjects, range 11 to 17 minutes, and the patients, 3 to 7 minutes

The mean maximum perceived dyspnea at maximum exercise as rated on the Borg scale was not different amongst the athletic group (7 50 ± 1 80), normal group (7 50 ± 1 73) or patient group (6 00 ± 1 73), p>0 05

Mean group dyspnea was examined as a function of the workload measured in watts (W) **[fig 9 1.a]** All groups demonstrated a curvilinear relationship of dyspnea to work There was no difference between mean group dyspnea values at quiet breathing of the athletic, normal and patient groups, p>0 05 It should be noted, though, that four of the seven patients did present with slight dyspnea at rest (2 with a dyspnea rating of 1, 2 with a dyspnea rating of 2) During the exercise test patients perceived significantly higher dyspnea than either the normals or athletes from the point when absolute workload was increased to 20 watts to the point when exercise was ceased, p<0 05 The athletes and normal subjects presented with similar dyspnea ratings from 0 W to 120 W, however, from 140 W to maximum exercise, normal subjects perceived higher levels of dyspnea than the athletic group for a given level of work, p<0 05

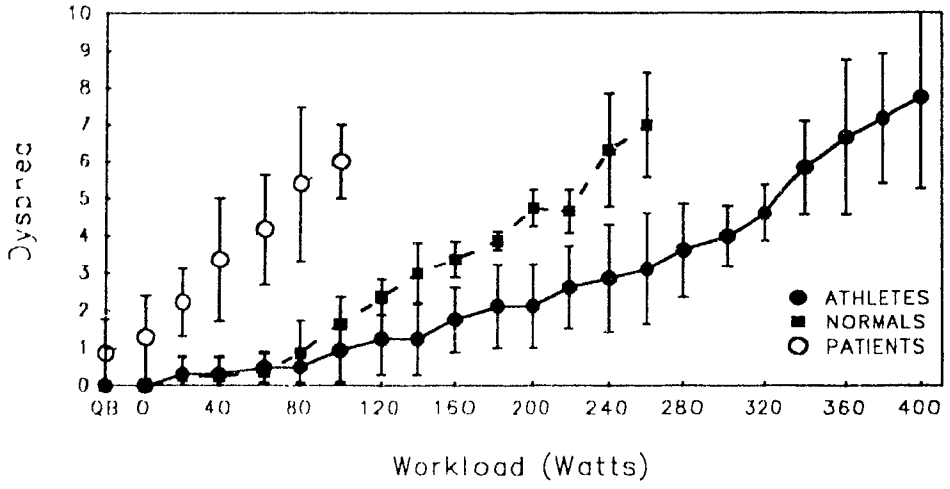


Figure 9 1 a Dyspnea plotted as a function of work, measured in watts Points represent group mean values ± 1 sd. QB represents quiet breathing.

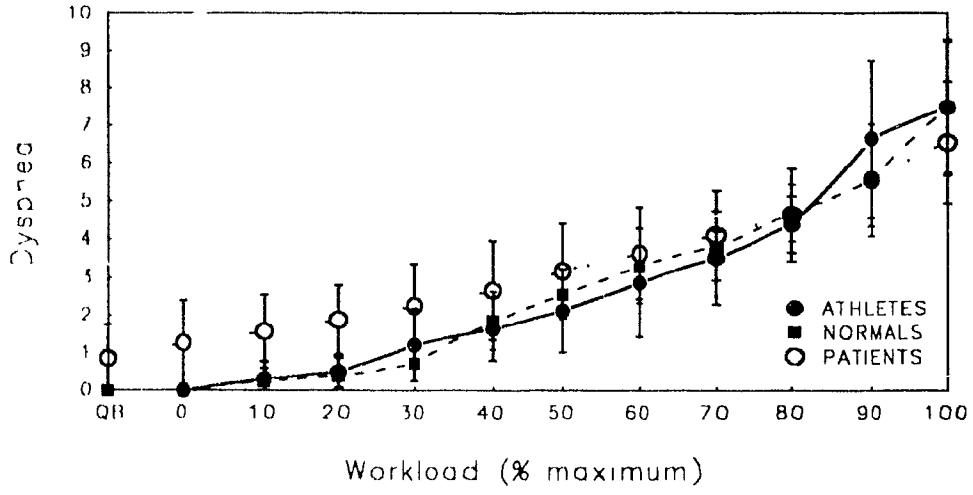


Figure 9.1 b Dyspnea plotted as a function of workload, normalized as % maximum Points represent group mean values ± 1 sd QB represents quiet breathing

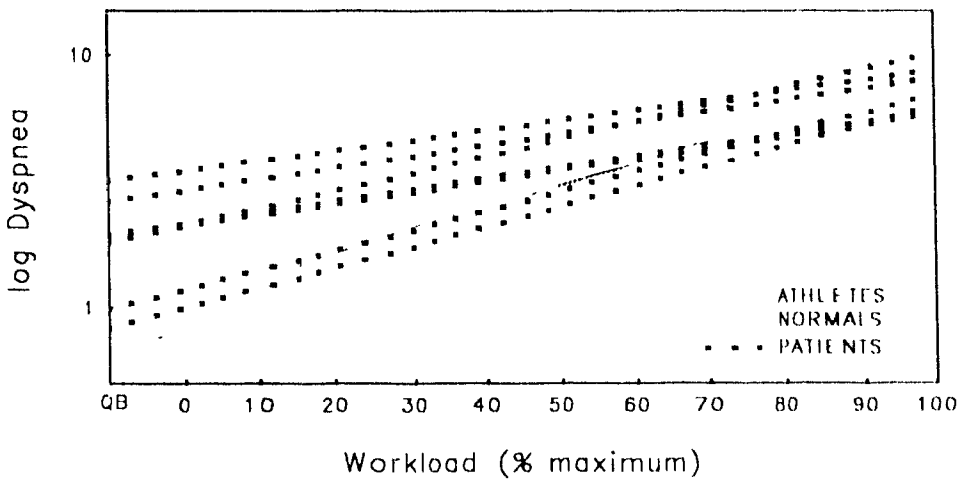


Figure 9 1.c Common log of Dyspnea plotted as a function of workload, normalized as % maximum. Lines represent the linear regressions for individual subjects.

9.2.2 Dyspnea as a Function of Workload (% Maximum)

Individual subject's dyspnea was examined as a function of workload, normalized as a percentage of the maximum workload achieved by that subject **[fig 9.1 b]** Workload was normalized in order to examine the dyspnea response observed relative to what percentage of the individual's maximum workload capacity he was exercising at

All subjects demonstrated a curvilinear relationship of dyspnea to normalized workload No difference existed between any groups from 0% to 100% maximum workload, $p>0.05$

The response rate of dyspnea to workload is defined as the rate of change of dyspnea per a given change in work The response rate was assessed by plotting the dyspnea scores on a common logarithmic (log) scale versus the % of achieved maximum workload A "1" was added to all dyspnea scores for all subjects to permit a logarithmic analysis This mathematical addition would not change the slope of the dyspnea/% maximum workload relationship but permitted the logarithmic analysis of 0 dyspnea values

The relationship of the common log of dyspnea to workload (% maximum) was linear in all subjects (means ± 1 sd of the regression coefficients were 0 95 ±0 05, 0 97 ±0 01, 0 96 ±0 04 for the athletes, normals and patients respectively) **[fig 9 1.c]** The slope of each individual regression line represents the response rate of dyspnea to work (% maximum) All athletes presented with similar response rates (0 83 ±0 09) Three of the four normals presented with very similar response rates (1 00 ±0 04) however one normal subject (N3) presented with a very low response rate (0 72) which was similar to the athletes The patient group presented with a significantly lower response rate (0.57 ±0.18) than either normals or athletes ($p<0.05$)

9.3 The Relationship of Minute Ventilation and Work

9.3 1 Minute Ventilation as a Function of Work

At rest, minute ventilation ($\dot{V}E$) was examined and no difference was found between the athletic group, 10 81 ±3 33 l/min, the normal group, 12.89 ±3 89 l/min, or patient group 12 70 ±4 19 l/min, $p>0.05$

Initially, $\dot{V}_E$ was plotted as a function of workload measured in absolute Watts **[fig 9.2.a]**. No difference in mean V_E existed between the normals and athletes at any levels of absolute workload up to 240 watts. At extremely high levels of work, greater than 240 watts, normals demonstrated significantly higher mean ventilation levels, $p<0.05$. Patients presented with similar mean $\dot{V}_E$ for the first five levels of measured work (0 to 80 W), however at >80 W, patients presented with significantly higher mean V_E than either normals or athletes, $p<0.05$.

When assessing the maximum value of V_E achieved at maximum exercise, athletes and normals reached similar values of V_E, 138.09 ± 29.49 l/min and 102.56 ± 33.51 l/min, whereas patients achieved lower values of V_E, 35.26 ± 16.20 l/min, $p<0.05$.

9.3.2 Normalized Minute Ventilation as a Function of Work

$\dot{V}_E$ was normalized for lung volume by dividing V_E by the individuals' Forced Vital Capacities (FVC). At quiet breathing, no difference existed between athletes and normals mean $\dot{V}_E/FVC$, 1.73 ± 0.59 and 2.41 ± 0.60, however, patients presented with a significantly higher mean V_E/FVC at rest, 5.22 ± 2.34, $p<0.05$. All groups, however, reached similar maximum V_E/FVC, 22.04 ± 4.90 sec., 19.13 ± 5.51 sec., 13.61 ± 4.94 sec. for the athletic, normal and patient group respectively, $p>0.05$.

Mean V_E/FVC versus absolute workload measured in watts (W) was plotted for each group **[fig 9.2.b]**. All groups demonstrated a curvilinear relationship of V_E/FVC to work. Patients presented with significantly higher V_E/FVC than athletes and normals at all levels of absolute workload. Athletes and normals presented with similar V_E/FVC from 0 to 140 watts. However at >160 watts, nearing the maximum workload achieved by normal subjects, the V_E/FVC of the normal group became significantly higher than the athletes, $p<0.05$.

9.3.3 Normalized Minute Ventilation as a Function of Workload (% Maximum)

The mean V_E/FVC of individual subjects was expressed as a function of the absolute workload in watts, normalized as a percentage of the maximum workload in watts achieved by each subject **[fig 9.2.c]**. All subjects demonstrated a curvilinear relationship of V_E/FVC

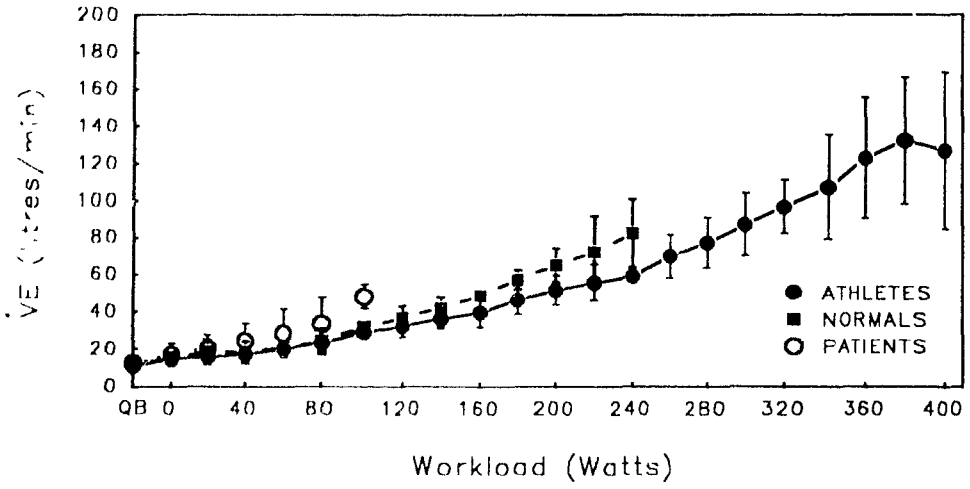


Figure 9 2 a Minute ventilation (VE) plotted as a function of work, measured in watts. Points represent group mean values ± 1 sd QB represents quiet breathing

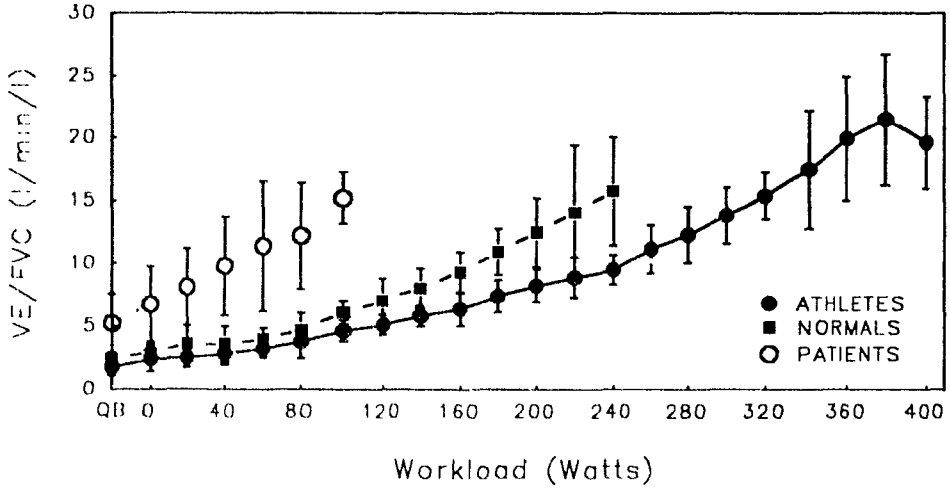


Figure 9 2 b $\dot{V}E/FVC$ plotted as a function of work, measured in watts Points represent group mean values ± 1 sd. QB represents quiet breathing

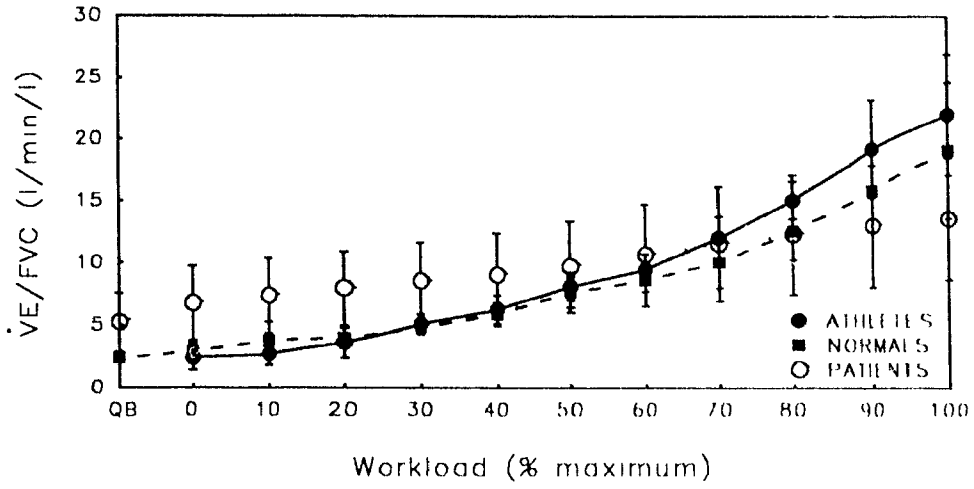


Figure 9 2 c V̇E/FVC plotted as a function of work, normalized as % maximum Points represent group mean values ± 1 sd QB represents quiet breathing

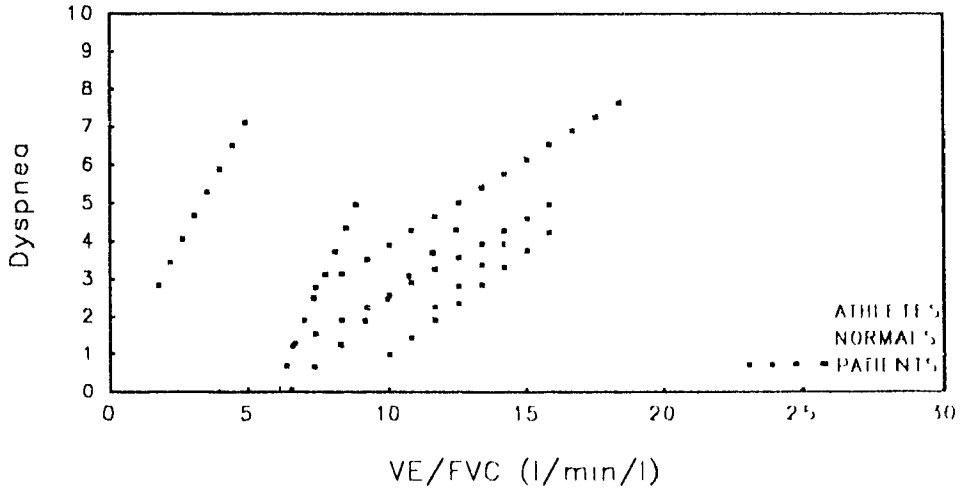


Figure 9.2 d Dyspnea plotted as a function of VE/FVC. Linear regression lines are presented for each individual subject

to work (% maximum) No difference existed between the mean $\dot{V}_E$/FVC of the athletic or normal groups at any level of normalized workload. Comparing the athletic and normal groups to the patients, the patient group demonstrated higher $\dot{V}_E$/FVC from 0 to 20%, $p<0.05$, but thereafter, similar V_E/FVC up to 100% of their maximum workloads, $p>0.05$

The rate of increase of $\dot{V}_E$/FVC with respect to normalized workload was examined by plotting V_E/FVC on a common logarithmic scale versus % maximum workload. All groups demonstrated a positive, linear relationship, mean correlation coefficients of 0.99 ± 0.00, 0.97 ± 0.02, 0.97 ± 0.03 for the athletic, normal and patient groups respectively. The rate of increase of V_E/FVC with increasing workload expressed as a % of maximum was similar between the normal and athletic groups, 0.84 ± 0.16 and 0.97 ± 0.11, however was significantly lower in the patient group, 0.36 ± 0.13, $p<0.05$.

9.4 Dyspnea as a Function of Minute Ventilation

Dyspnea was plotted as a function of V_E normalized by FVC for each individual subject **[fig 9.2 d]** All subjects demonstrated a positive, linear relationship between dyspnea and V_E/FVC, mean correlation coefficients of 0.97 ± 0.03, 0.97 ± 0.02 and 0.91 ± 0.09 for the athletic, normal and patients groups respectively The mean response rates of dyspnea to changes in V_E/FVC (slopes of the regression lines) were also similar; 0.34 ± 0.08, 0.45 ± 0.07, 0.87 ± 0.52 for the athletic, normal and patient groups respectively, $p>0.05$ However, as observed, a large variation in response rates existed within the patient group The range of response rates within the patient group was 0.41 to 1.80. This demonstrates that although some patients did present with similar response rates as the athletes and normals, other patients demonstrated much higher dyspnea response rates to increasing ventilation normalized for lung size **[fig 9.2 d]**

It is intriguing to see that as a group, patients, normals and athletes can reach very different levels of ventilation **[fig 9.2.a]**, however, when that ventilation ($\dot{V}_E$) is normalized for lung size (V_E/FVC), significant overlap exists within individual subjects' dyspnea responses independant if the subject is an elite athlete, normal or COPD patient.

9.5 Minute Ventilation Normalized as a Percentage of Reserve Capacity

9.5.1 $\dot{V}_E$/MVV as a Function of Work

In order to determine what percentage of their maximum dynamic ventilatory capacity was being utilized throughout the exercise test, subject's V_E was normalized as a percentage of their predicted maximum voluntary ventilation (MVV) At quiet breathing, the athletic and normal groups presented with similar mean V_E/MVV, 4 94 ± 1 74% and 7 47 ±2 39% respectively, while the patient group presented with a significantly higher mean V_E/MVV at rest, 32 18 ± 18 60%, $p<0\ 05$ At maximum exercise, all groups demonstrated similar mean maximum V_E/MVV, 58 15 ± 14 67%, 59 26 ± 20 00% and 81 24 ± 32 72%, for the athletic, normal and patient groups respectively Once again, a large variance existed within the patient group, range 45 38% to 135 75% This indicated that while some patients were utilizing similar percentages of their maximum ventilatory capacity as the athletes and normals during maximum exercise, other patients minute ventilatory levels were far in excess of the defined maximum sustainable ventilatory level of 60% MVV

Group mean V_E/MVV values were plotted versus absolute workload measured in watts (W) **[fig 9 3 a]**. All groups demonstrated a curvilinear relationship of V_E/MVV to absolute work Patients presented with significantly higher V_E/MVV at all levels of absolute work, $p<0\ 05$ Athletes and normals presented with similar V_E/MVV from 0 W to 120 W However, at > 120 W, normals'mean V_E/MVV was significantly higher at each level of work up to maximum workloads, $p<0\ 05$

9.5.2 $\dot{V}_E$/MVV as a Function of Workload (% maximum)

Individual subject's mean V_E/MVV were expressed as a function of workload normalized as a percentage of the maximum workload achieved by each subject **[fig 9 3 b]** Please refer to section 9 2.2 for the purpose for normalizing workload in this manner

All subjects demonstrated a curvilinear relationship of V_E/MVV to normalized work (% maximum) No difference existed between the mean V_E/MVV of the athletic or normal groups at any level The patient group demonstrated significantly higher mean V_E/MVV only up to 40% of maximum work

The rate of increase of V_E/MVV with respect to normalized workload was examined

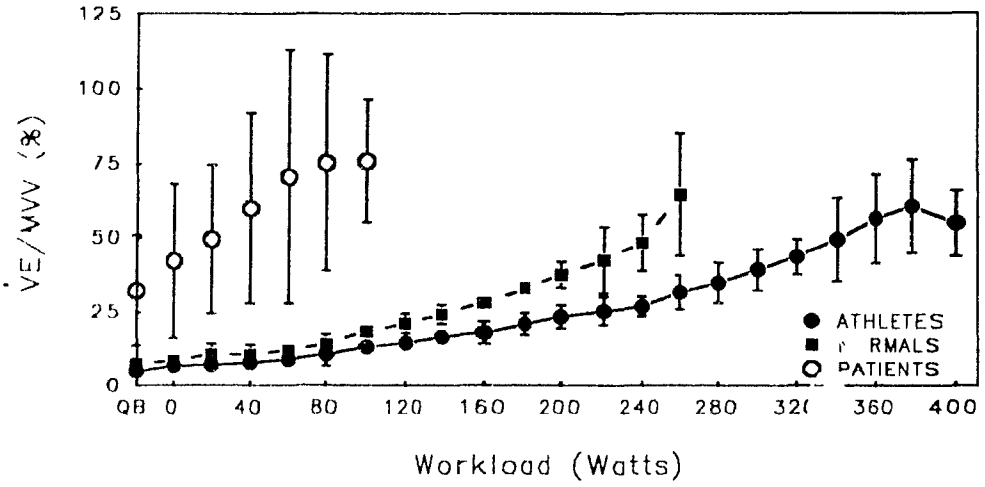


Figure 9.3.a V̇E/MVV (%) plotted as a function of work, measured in watts. Points represent mean values ± 1 sd. QB represents quiet breathing.

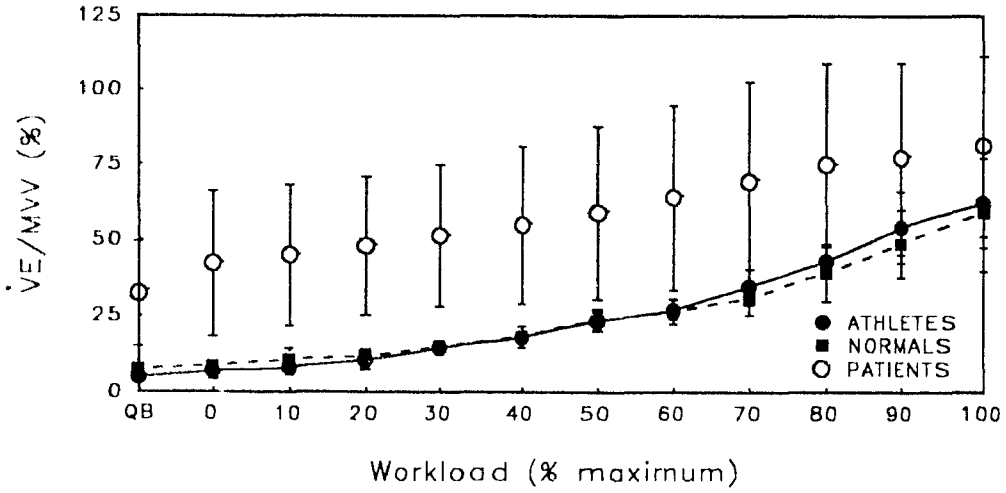


Figure 9.3.b VE/MVV (%) plotted as a function of workload, normalized as a % maximum. Points represent group mean values ± 1 sd QB represents quiet breathing.

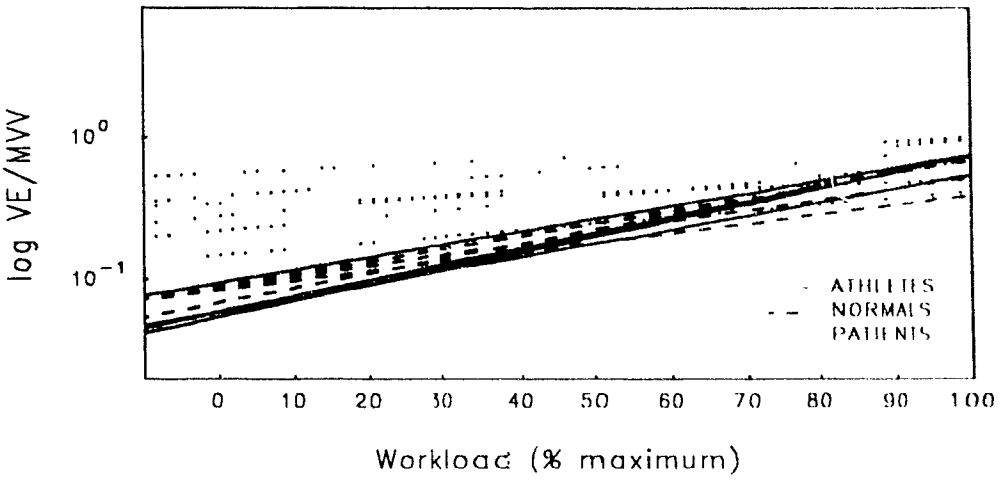


Figure 9.3.c Common log of $\dot{V}E/MVV$ plotted as a function of workload, normalized as % maximum. Lines represent the linear regressions for individual subjects.

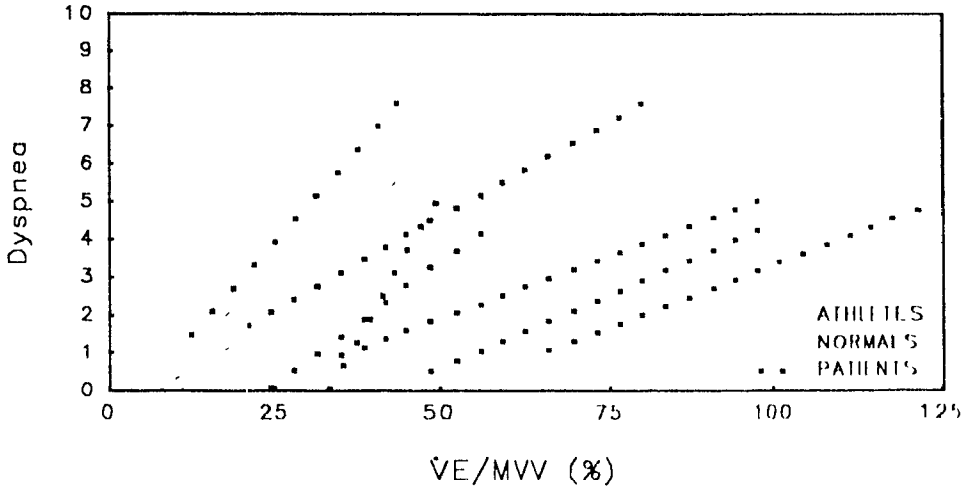


Figure 9.3.d Dyspnea plotted as a function of $\dot{V}E/MVV$ (%). Linear regression lines are presented for each individual subject.

by plotting the common logarithmic relationship of $\dot{V}E/MVV$ versus normalized workload (% maximum) for each individual subject **[fig 9.3.c]** All groups demonstrated positive linear relationships, mean correlation coefficients of 0 99 ±0 00, 0.97 ±0 02 and 0 96 ±0 03 for the athletes, normals and patients respectively The rate of increase of $\dot{V}E/MVV$ was similar between the normal and athletic groups, 0 01 ±0 00 and 0 01 ±0 00, however patients presented with significantly lower mean rates of increase of $\dot{V}E/MVV$ with increasing levels of normalized workload, 0 004 ±0 00, $p<0\ 05$

9.6 Dyspnea as a Function of $\dot{V}E/MVV$

Dyspnea was plotted as a function of $\dot{V}E/MVV$ for individual subjects **[fig 9.3.d]** All subjects demonstrated a positive linear relationship between dyspnea and $\dot{V}E/MVV$; mean group correlation coefficients of 0 97 ±0 03, 0 97 ±0 02 and 0 92 ±0 08 for the athletes, normals and patients respectively Response rates of dyspnea to increases in $\dot{V}E/MVV$ (slopes of the regression lines) were also similar between athletic, normal and patient groups, 0 12 ±0 03 0 15 ±0 02 and 0 13 ±0.09, $p>0\ 05$ Similar to the observed dyspnea responses to $\dot{V}E/FVC$ of subjects, overlap also existed between individual subject's response rates when dyspnea was related to ventilation, normalized by their ventilatory reserve capacity

9 7 The Relationship of Dyspnea to Pleural Pressure Changes

The analysis of the relationship of dyspnea to pleural pressure changes consists of regression analysis of the relationships between changes in individual subject's dyspnea levels to changes in inspiratory pleural pressure swings (ΔPes) Values of ΔPes are also compared, both at quiet breathing and at maximum exercise for each of the three subject groups

9 7 1 ΔPes Normalized by Maximal Inspiratory Pressure (MIP)

Previous investigators have normalized pleural pressure changes by expressing ΔPes as a percentage of the Maximal Inspiratory Pressure (MIP). At quiet breathing,

athletes and normal subjects presented with similar ΔPes/MIP, 0 04 ±0 01 and 0 04 ±0 01, p<0 05. Patients were generating significantly higher ΔPes/MIP at quiet breathing, 0 18 ±0.08 At maximum exercise, the athletic and normal groups presented with similar mean ΔPes/MIP, 0 28 ±0 09 and 0 25 ±0 04 The patient group presented with a significantly higher mean ΔPes/MIP, 0 54 ±0 21, p<0 05 As noted, a large variance existed within the patient group. Patient 6 reached a maximumΔPes/MIP value of 0 27, similar to both athletes and normals Whereas, at the other extreme, P2 reached a maximum ΔPes/MIP of 0 92.

Dyspnea was plotted as a function of ΔPes/MIP for each individual Individual regression lines for this relationship are presented **[fig 9 4 a]** All subjects demonstrated a positive, linear relationship between Dyspnea and ΔPes/MIP, mean group regression coefficients of 0 97 ±0 01, 0 97 ±0 02, 0 87 ±0 11 for the athletic, normal and patient groups respectively This relationship represents the subject's dyspnea response to pleural pressure changes.

Much variation existed, within and between groups when dyspnea responses to pleural pressure changes were compared Given this variation, the data was analyzed according to the following criteria Within each group, a cut off response rate of 40 was set Therefore any subjects with dyspnea responses above 40 were classified as high dyspnea responders, whereas any subjects within that group with dyspnea responses less than 40 were deemed low dyspnea responders

9.7.1.1 Dyspnea Response to ΔPes/MIP of Athletes

All four athletes presented with dyspnea responses which classified them as low dyspnea responders, mean group dyspnea response of 28 4 ±6 4

9.7.1.2 Dyspnea Response to ΔPes/MIP of Normals

Two of the four normals (N1, N2) presented with high dyspnea responses, significantly greater than the athletes, mean response rate of 45 14 ±1 46, p<0 05 The two

remaining normals (N3,N4) presented with low response rates of 23 44 and 29 06, similar to that of the athletic group

9.7 1.3 Dyspnea Response to ΔPes/MIP of Patients

All patients presented with dyspnea responses which were classified as low responses, group mean of 17 03 ±9 60, similar to the athletic group, normal subject low dyspnea responders, but significantly lower than the two normal subjects who were classified as high dyspnea responders, $p<0.05$

What was interesting was that within the patient group, a wide range of responses did exist In fact, five of the seven patients (P1, P2, P4, P5, P7) presented with very low response rates, mean of 11 69 ±3 33 while the remaining two patients (P3,P6) presented with much higher response rates, mean 30 37 ±3 15 So, in terms of the definition of high and low response, as a group, the patients were defined as low responders, however within the patient group, it appears that two distinct response patterns also existed

9.7.2 ΔPes Normalized by the Maximum Pressure Generating Capacity of the Inspiratory Muscles during Exercise

ΔPes was expressed as a function of P_{cap} At quiet breathing, the athletic and normal groups presented with similar mean $\Delta Pes/P_{cap}$ of 0 05 ±0 02 and 0 04 ±0 01 respectively, $p>0.05$ The patient group demonstrated significantly higher $\Delta Pes/P_{cap}$ at quiet breathing, 0 21 ±0 09, $p<0.05$ At maximum exercise, the athletic and normal groups demonstrated similar mean $\Delta Pes/P_{cap}$, 0 45 ±0 17 and 0 34 ±0 03, $p<0.05$ Patients presented with significantly higher mean $\Delta Pes/P_{cap}$ when compared to the normal group, $p<0.05$, but similar mean $\Delta Pes/P_{cap}$ when compared to the athletic group, 0 63 ±0 24, $p>0.05$ However, a large variance existed within the patient group P6 reached a maximum $\Delta Pes/P_{cap}$ value of 0 34, similar to both athletes and normals Whereas, at the other extreme, P2 reached a maximum $\Delta Pes/P_{cap}$ of 1 01 far in excess of that achieved by any normal or athlete

The relationship between dyspnea and $\Delta Pes/P_{cap}$ was assessed Individual regression lines of this relationship for each individual subject are plotted **[fig 9 4 b]** A

positive, linear relationship existed between dyspnea and ΔPes/P_{cap} for all subject groups, mean correlation coefficients of 0 95 ±0 01, 0 95 ±0 02, 0 87 ±0 11 for the athletes, normals and patients respectively

The dyspnea response rates of both athletes and normals were statistically lower when using P_{cap} normalization for ΔPes versus MIP normalization, $p<0\ 05$ Although the dyspnea response rates were lower for both low and high responding patients with P_{cap} normalization, the differences in response rates when compared to MIP normalization were not significant, $p>0\ 05$

Similar to observations made with MIP normalization, a lot of variation existed, within and between groups when dyspnea responses to pleural pressure changes, normalized by P_{cap}, were compared

In order compare varying dyspnea response rates, not only between groups but within groups as well, a new lower cut off response rate of 25 was set, to compensate for the statistically lower response rates observed in athletes and normals with P_{cap} normalization Therefore any subjects with dyspnea responses above 25 were classified as high dyspnea responders, whereas any subjects with dyspnea responses less than 25 were deemed low dyspnea responders

9.7 2 1 Dyspnea Response to ΔPes/P_{cap} of Athletes

All athletes (A1, A2, A3, A4) presented with similar dyspnea responses below 25, mean 18 30 ±3 50, and therefore were classified as "low dyspnea responders".

9.7 2 2 Dyspnea Response to ΔPes/P_{cap} of Normals

Two of the four normals (N1, N2) presented with dyspnea responses above 25, mean value of 27 45 ±1 48, which is significantly higher than the mean response of the athletic group, $p<0\ 05$ Therefore, N1 and N2 will be referred to as "high dyspnea responders" in all subsequent analysis Two of the four normals (N3, N4) presented with similar dyspnea responses below 25 as the athletes, mean of 18 70 ±0 26, $p>0\ 05$ and therefore are referred to as "low dyspnea responders" in all subsequent analysis.

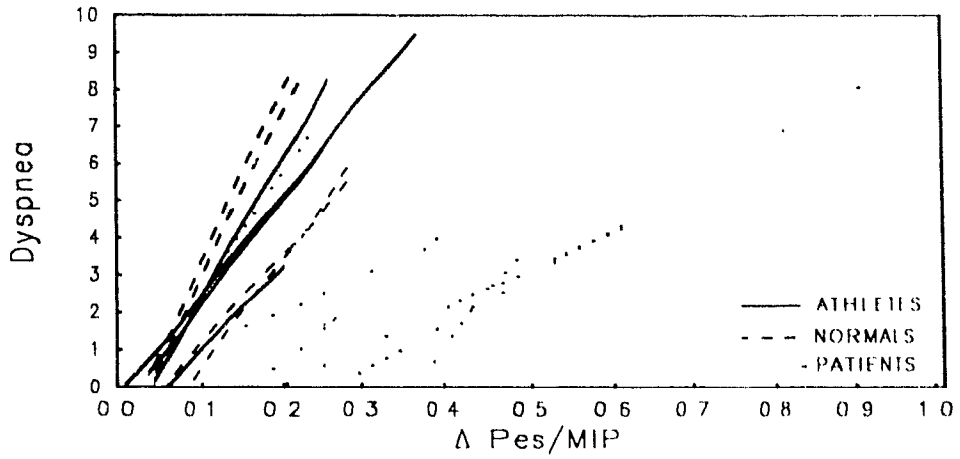


Figure 9.4.a Dyspnea is plotted as a function of ΔPes/MIP Lines plotted represent the linear regression lines of each individual subject for this relation ship

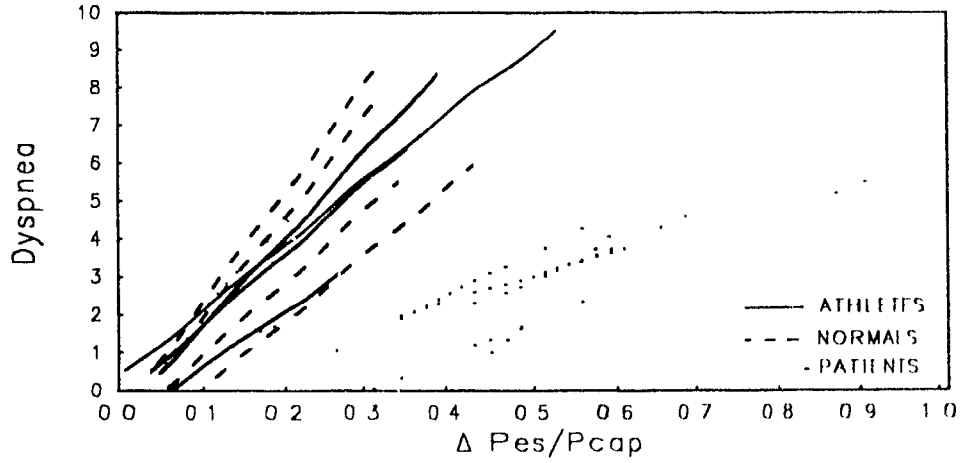


Figure 9.4.b Dyspnea is plotted as a function of ΔPes/Pcap. Lines plotted represent the linear regression lines of each individual subject for the presented relationship

9 7 2 3 Dyspnea Response to ΔPes/Pcap of Patients

As a group, the COPD patients all presented with dyspnea response rates below 25 It is observed, though, that much variation in dyspnea response existed within this patient group In fact, five of the seven patients (P1,P2,P4,P5,P7) presented with extremely low dyspnea responses, statistically lower than the athletic group or low responding normals, mean 8 85 ± 1 51, $p<0.05$ It was therefore proposed that although all patients presented with a "low dyspnea response" given the above mentioned criteria, that patients as a distinct group may display both "low" and "high" dyspnea responses Indeed, the remaining two patients (P3,P6) presented with statistically higher dyspnea response rates, mean 22 53 ± 0 15, when compared to the lower responding patients

Future results focus upon the respiratory muscle coordination and whether an individual subject's adopted breathing pattern appears to have any relationship to his observed dyspnea response rate to changes in pleural pressure normalized by Pcap In order to facilitate this analysis, and based upon the above results the following definition will be used throughout the remainder of this thesis Within the athletic and normal groups, all athletes are termed low dyspnea responders (LDR), and N3 and N4 are also referred to as low dyspnea responders (LDR) N1 and N2 will be referred to as high dyspnea responders The patient group will be treated as distinct, therefore within that group P1,P2,P4,P5,P7 will be referred to as low dyspnea responders whereas P3,P6 will be referred to as high dyspnea responders

9.7 3 Validity of Regression Analysis in Predicted Maximum Achieved ΔPes/Pcap Values

The actual measured maximum ΔPes/Pcap achieved by individual subjects was compared to that predicted by linear regression analysis All subjects' actual maximum ΔPes/Pcap values were within 0 10 of that predicted by linear regression (the dyspnea response) with the following exceptions **[fig 9 5]**

1 N4 The regression line overestimates his maximum achieved ΔPes/Pcap by 0 17

2 P1 The regression line overestimates his maximum achieved ΔPes/Pcap by 0 26

Both of these subjects demonstrated a change in their response patterns midway

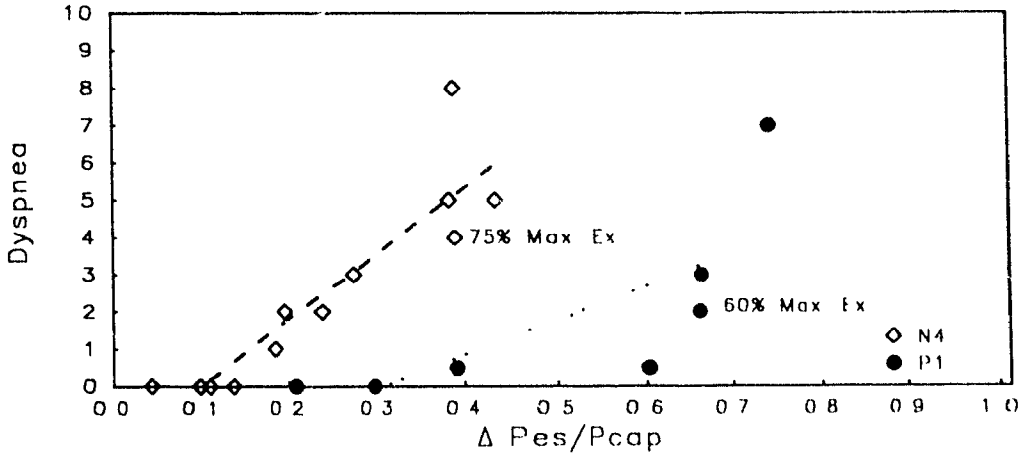


Figure 9 5 Individual data points and linear regression lines are presented for normal subject 4 (N4) and patient 1 (P1) See text for description.

through the exercise test At approximately 75% of his maximum exercise level achieved, N4 no longer achieved significant increases in ΔPes/Pcap, despite further increasing dyspnea P1 demonstrated a similar pattern, whereby at 60% of his maximum exercise level achieved, dyspnea increased at an accelerated rate despite smaller changes in ΔPes/Pcap

9.8 Analysis of "Pre-Inspiratory Flow" Pressure Generation

A combined four parameter graph is presented in **Figure 9.6** For each of the four relationships presented, the regression lines for each individual subject are presented. In the upper right quadrant, the relationship of Dyspnea to end expiratory pleural pressure (EEP) measured in cmH20 is plotted The lower right quadrant plots individuals' relationships between EEP and the rate of change of pleural pressure (prior to the onset of inspiratory flow) with respect to time $(\Delta Pes/\Delta t)_{PRE}$, measured in cmH20/second The upper left quadrant plots Dyspnea as a function of the rate of change of gastric pressure (prior to the onset of inspiratory flow) with respect to time $(\Delta Pga/\Delta t)_{PRE}$, measured in cmH20/second. The lower left quadrant plots the relationships between $(\Delta Pes/\Delta t)_{PRE}$ versus $(\Delta Pga/\Delta t)_{PRE}$. Numerical values (mean ± sd) for each subject for each of the four variables at quiet breathing and at maximum exercise are presented in **Table 9 3**

9.8.1 Dyspnea versus EEP [Figure 9 6, upper right]

Changes in EEP can result from changes in either end expiratory lung volume (EELV), increased expiratory muscle recruitment or a combination of both Observed changes in EEP occur during exercise, both in normal, athletic and COPD subjects These changes in EEP will directly effect the magnitude of the load placed upon the inspiratory muscles for the next inspiratory effort The purpose of the following analysis was not to imply a causal effect between EEP and dyspnea, but rather as a method to infer how much load was placed upon the inspiratory muscles and whether changes in this loading pattern affected dyspnea

At quiet breathing, no difference existed between the measured EEP of athletes and normals, -2 80 ±2 37 cmH20 and -5 82 ±3 98 cmH20. Patients as a group presented with

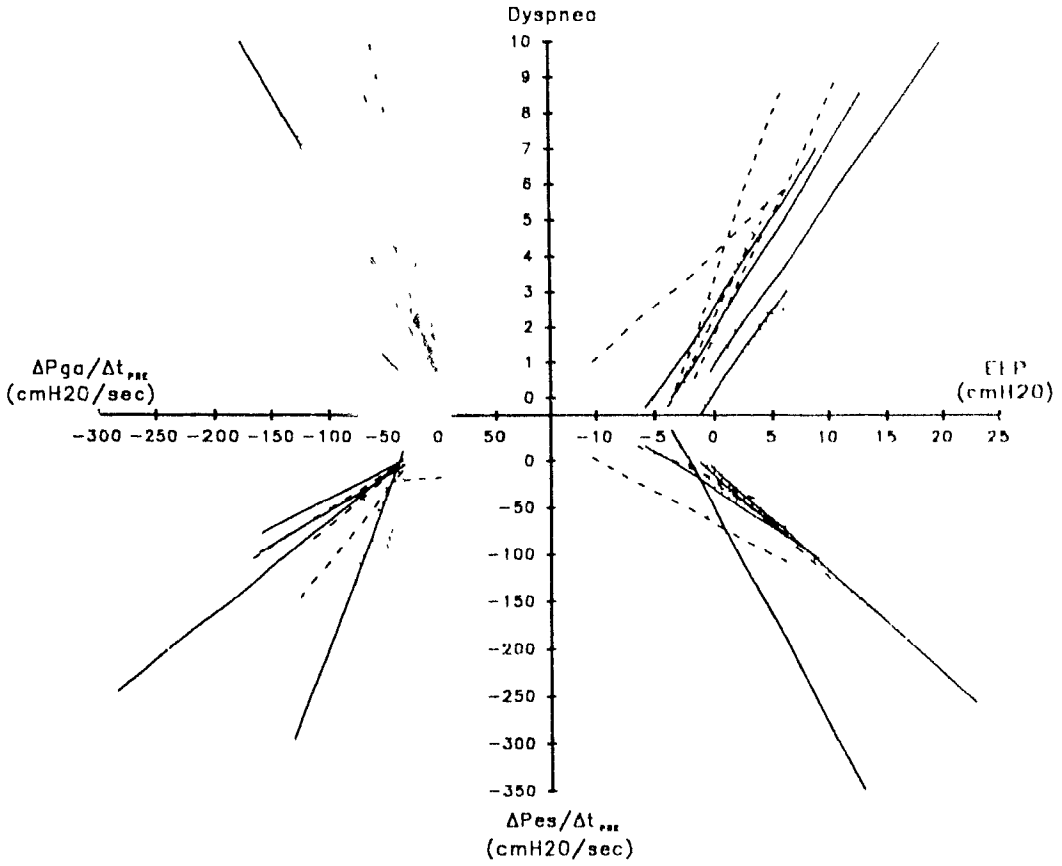


Figure 9 6 Lines plotted represent the linear regression for each individual subject for each of the four presented relationships Solid lines (———) represent athletes, dashed lines (------) represent normal subjects and dotted lines (·) represent COPD patients See text for a detailed description of each plot

SUBJECT	QB Dyspnea	MAX Dyspnea	QB EEP (cmH20) mean ±sd	MAX EEP (cmH20) mean ±sd	QB ΔPes Δt_{exE} (cmH20 sec) mean ±sd	MAX ΔPes Δt_{exE} (cmH20 sec) mean ±sd	QB ΔPga Δt_{exE} (cmH20 sec) mean ±sd	MAX ΔPga Δt_{exE} (cmH20 sec) mean ±sd
A1	0	9 5	-0 41 ±0 42	22 84 ±4 24	0 00 ±0 00	-228 89 ± 27 59	0 00 ± 0 00	-188 74 ±42 54
A2	0	4 0	-1 39 ±0 60	6 31 ±3 29	0 00 ±0 00	-34 25 ± 39 15	0 00 ± 0 00	-84 50 ±30 70
A3	0	6 0	-5 68 ±0 44	9 01 ±3 47	0 00 ±0 00	-127 90 ± 75 13	0 00 ± 0 00	-96 74 ±34 42
A4	0	7 0	-3 72 ±0 76	12 94 ±4 01	0 00 ±0 00	-364 57 ±130 21	0 00 ± 0 00	-45 84 ± 7 35
N1	0	9 0	-3 42 ±1 28	5 91 ±2 52	0 00 ±0 00	-91 96 ± 43 87	0 00 ± 0 00	-64 53 ±57 77
N2	0	8 0	-1 99 ±0 50	10 82 ±1 22	0 00 ±0 00	-140 02 ± 48 87	0 00 ± 0 00	-68 51 ±24 74
N3	0	5 0	-10 90 ±0 48	6 03 ±4 48	0 00 ±0 00	-101 26 ± 45 26	0 00 ± 0 00	-104 26 ±46 98
N4	0	8 0	-6 95 ±0 26	3 14 ±4 50	0 00 ±0 00	-37 01 ± 25 89	0 00 ± 0 00	27 98 ±29 50
P1	0	7 0	-0 74 ±0 29	11 45 ±3 25	0 00 ±0 00	-268 30 ± 39 41	0 00 ± 0 00	-53 68 ±43 98
P2	0	7 0	-1 16 ±0 72	14 96 ±4 36	0 00 ±0 00	-192 24 ± 27 52	0 00 ± 0 00	-130 98 ±28 18
P3	0	5 0	-3 18 ±1 41	-0 20 ±2 66	-93 46 ±12 43	-90 04 ± 2 21	-12 22 ±39 57	-4 85 ±44 34
P4	1 0	5 0	-1 09 ±0 96	16 79 ±1 00	-20 12 ±11 63	-149 79 ± 23 25	-1 13 ±11 25	-46 72 ± 7 56
P5	1 0	5 0	1 62 ±1 13	5 54 ±0 86	-30 12 ±6 49	-77 60 ± 8 20	-25 27 ± 6 51	-51 24 ± 6 19
P6	2 0	9 0	-0 95 ±1 02	6 92 ±2 92	0 00 ±0 00	-58 93 ± 22 64	0 00 ± 0 00	-32 06 ±19 78
P7	2 0	4 0	-0 20 ±0 20	9 02 ±1 12	0 00 ±0 00	-102 90 ± 12 84	0 00 ± 0 00	-36 44 ± 4 71

Table 9.3

similar results to the athletes, -0 81 ± 1 42 cmH20, but higher EEP than the normals, $p<0.05$

At maximum exercise, the athletes, normals and patients presented with a wide range of EEP (9 02 cmH20 to 22 84 cmH20, 3 14 cmH20 to 10 82 cmH20, -0 20 cmH20 to 16 79 cmH20) Although group means were not statistically significant, it was observed that within the patient group, 4 of those patients previously defined as low responders (P1,P2,P4,P7) presented with higher EEP (mean EEP of 13 05 ± 3 49cmH20) when compared to the two patients termed high responders (P3,P6)

9.8.1.1 Dyspnea Response to EEP of Athletes

The athletic group presented with a strong linear relationship between dyspnea and EEP, mean group correlation coefficient ± 1 sd of 0 93 ±0 02, and a mean dyspnea response to EEP of 0 48 ± 0 03

9.8.1.2 Dyspnea Response to EEP in Normals

All normal subjects presented with a positive relationship between dyspnea and EEP, however, the mean group correlation coefficient of the group was significantly lower than the athletic group, 0 78 ±0 06, $p<0 05$

Three normal subjects, N1,N2,N4, presented with higher dyspnea responses to EEP when compared to the athletes, range of 0 63 to 0 91 while N3 presented with a low dyspnea response to EEP, similar to the athletes, 0 29

9.8.1.3 Dyspnea Response to EEP in Patients

As a group, a large variation in dyspnea response to EEP existed Five of the seven patients (P1,P2,P4 ,P6,P7) demonstrated a strong linear relationship between dyspnea and EEP, mean correlation coefficient of 0 88 ±0 11 P3, a high responding patient, demonstrated a weak relationship between dyspnea and EEP, correlation coefficient of 0 58 P5 presented with no significant correlation Observing responses for those patients who did present with a strong relationship, those patients termed low responders (P1,P2,P4,P7) had a similar low dyspnea response as observed in the athletes, mean

response of 0 36 ± 0 17 The remaining patient, P6, presented with a much higher mean response rate of 0 84 ± 0 25 when compared to the athletes, N3 and P1,P2,P4,P7 This value was similar to the dyspnea response measured in N1,N2 and N4

9 8 2 EEP versus $(\Delta Pes/\Delta t)_{PRI}$ [figure 9.6, lower right]

At quiet breathing all athletes and normals presented with 0 $\Delta Pes/\Delta t_{PRE}$ (ie. no negative pleural pressure swing preceded the onset of inspiratory flow) Four of the seven patients (P1,P2,P6,P7) also presented with 0 $\Delta Pes/\Delta t_{PRE}$ at quiet breathing P3 and P5 presented with negative mean $\Delta Pes/\Delta t_{PRI}$ (-93 46 ± 12 43 cmH20/sec and -30 12 ± 6 49 cmH20/sec), whereas P4 presented with very small and inconsistent negative pleural pressure swings prior to the onset of inspiratory flow

At maximum exercise, two of the four athletes (A1 & A4) presented with very rapid mean $\Delta Pes/\Delta t_{PRI}$ (-281 73 ± 74 73 cmH20/sec) A3 presented with a lower mean $\Delta Pes/\Delta t_{PRI}$ of -127 90 cmH20/sec however he ceased exercise at 80% of his maximum workload

In the normal subjects, three of the four (N1,N2,N3) presented with similar, slower $\Delta Pes/\Delta t_{PRI}$, (-111 08 ± 25 49 cmH20/sec) N4 presented with a very slow $\Delta Pes/\Delta t_{PRE}$ of -25 89 cmH20/sec, with a very large variance about the mean.

In the patients, a wide range of $\Delta Pes/\Delta t_{PRI}$ were observed at maximum exercise. Three of the patients, all low responders, (P1, P2, P4) presented with very rapid $\Delta Pes/\Delta t_{PRI}$, similar to the athletes (mean rate of -203 44 ± 60 04 cmH20/sec) P5 presented with a slower $\Delta Pes/\Delta t_{PRI}$ of -77 63 ± 8 20 P3 and P7 presented with similar $\Delta Pes/\Delta t_{PRE}$ of -90 04 ± -2 21 and -102 9 ± 12 84. Finally P6 presented with the lowest $\Delta Pes/\Delta t_{PRI}$, -58 93 ±22.64.

9.8.2 1 The Relationship of EEP to $\Delta Pes/\Delta t_{PRI}$

All athletes and normals demonstrated a strong linear relationship between EEP and $\Delta Pes/\Delta t_{PRI}$, (mean correlation coefficients of 0 92 ± 0 05 and 0 87 ± 0 08 respectively) Four patients (P1,P2,P4,P7), all defined as low responding patients, also demonstrated a very strong correlation between EEP and $\Delta Pes/\Delta t_{PRE}$, mean correlation coefficient of 0 98 ± 0 01. P5 and P6 demonstrated a weaker, yet still positive relationship between EEP and

$\Delta Pes/\Delta t_{PRE}$, mean correlation coefficient of 0 67 ±0 07, while P3 (high responder) presented with a poorer correlation coefficient of 0 35

9.8.3 Dyspnea versus $\Delta Pga/\Delta t_{PRE}$ [fig 9.6, upper left]

At quiet breathing, neither athletes or normals demonstrated negative gastric pressure swing prior to the onset of inspiratory flow Similarly, four patients (P1,P2,P6,P7) also demonstrated no negative gastric pressure swing preceding flow The remaining patients (P3,P4,P5) presented with inconsistent patterns of negative gastric pressure swings prior to the onset of flow with values of $\Delta Pga/\Delta t_{PRE}$ of -12 22 ±39 57 cmH20/sec, -1 16 ±11.25 cmH20/sec, -25 27 ±6 51 cmH20/sec, respectively

At maximum exercise, all subjects except for one normal (N4), presented with negative gastric pressure swings prior to the onset of inspiratory flow The athletes presented with a high variation in $\Delta Pga/\Delta t_{PRE}$, range -45 84 ±7 35 (A4) to -188 74 ±42 54 (A1). The normals also presented with a large range of values, +27 98 ±29 50 (N4) to -104 26 ±46 98 (N3) Patients also presented with large ranges of, and sometimes inconsistent patterns reflected by a large standard deviation, of $\Delta Pga/\Delta t_{PRE}$ (-4 85 ±44 34 (P3) to -130 98 ±28 18 (P2))

9.8.3.1 Dyspnea Response to $\Delta Pga/\Delta t_{PRE}$ of Athletes

A direct linear relationship existed between dyspnea and $\Delta Pga/\Delta t_{PRE}$ for all athletes, mean group correlation coefficient of 0 90 ±0 04 All athletes also presented with similar low dyspnea responses to $\Delta Pga/\Delta t_{PRE}$, -0 06 ±0 02

9.8.3 2 Dyspnea Response tc $\Delta Pga/\Delta t_{PRE}$ of Normals

Three normal subjects (N1,N2,N3) presented with strong positive relationships between dyspnea and $\Delta Pga/\Delta t_{PRE}$, mean correlation coefficient of 0 80 ±0 03 N4 presented with an insignificant correlation between dyspnea and $\Delta Pga/\Delta t_{PRE}$ Looking within the normal group, the two normal subjects defined previously as high responders (N1,N2) presented with higher dyspnea responses to $\Delta Pga/\Delta t_{PRE}$ than the athletic group, -0 14 and -

0 10, p<0 05 N3 presented with a low dyspnea response similar to the athletes, -0.05

9 8 3 3 Dyspnea Response to $\Delta Pga/\Delta t_{PRI}$ of Patients

All patients demonstrated a positive linear relationship between dyspnea and $\Delta Pga/\Delta t_{PRI}$, mean group correlation coefficient of 0 84 ± 0 11 Three patients, P2,P4,P7, (all low responders) presented with similar low mean dyspnea response to $\Delta Pga/\Delta t_{PRE}$ when compared to the athletic group, -0 06 ± 0 02 Three patients (P1,P5,P6) presented with similar dyspnea responses when compared to high responding normal subjects (N1,N2), -0 14 ± 0 02 Although P3 demonstrated a positive dyspnea response to $\Delta Pga/\Delta t_{PRE}$ of 0.33, the correlation coefficient of the relationship was only 0 69

9 8 4 The Relationship of $\Delta Pes/\Delta t_{PRI}$ to $\Delta Pga/\Delta t_{PRI}$ [fig 9.6 lower left]

The relationship of $\Delta Pes/\Delta t_{PRI}$ to $\Delta Pga/\Delta t_{PRE}$ indicates the contribution of the rate of the gastric pressure swing to the rate of the pleural pressure swing and is defined as the Pdi ratio A ratio of 1 indicates that for every change in the rate of the gastric pressure swing, an equal and similar directional change in the rate of the pleural pressure swing occurred (Pdi = 0), whereas a ratio of -1 indicates that a large Pdi is being generated

9.8 4 1 $\Delta Pes/\Delta t_{PRI}$ to $\Delta Pga/\Delta t_{PRI}$ of Athletes

All athletes demonstrated a positive linear relationship of $\Delta Pes/\Delta t_{PRE}$ to $\Delta Pga/\Delta t_{PRE}$, mean group correlation coefficient of 0 90 ± 0 08 Three athletes (A1,A2,A3) presented with very low Pdi ratios, mean 1 03 ± 0 25 whereas A4 presented with a higher Pdi ratio of 4 15

9 8 4 2 $\Delta Pes/\Delta t_{PRI}$ to $\Delta Pga/\Delta t_{PRI}$ of Normals

Three normal's (N1,N2,N3) demonstrated a positive linear relationship of $\Delta Pes/\Delta t_{PRE}$ to $\Delta Pga/\Delta t_{PRI}$, mean correlation coefficient of 0 94 ± 0 05 No correlation existed between $\Delta Pes/\Delta t_{PRI}$ and $\Delta Pga/\Delta t_{PRI}$ for N4 N1 and N2 presented with a mean Pdi ratio of 1.67 ± 0 43 N3 presented with a low Pdi ratio, similar to the athletes (A1,A2,A3) of 1 03

9.8.4.3 $\Delta Pes/\Delta t_{PRE}$ to $\Delta Pga/\Delta t_{PRE}$ of Patients

All patients demonstrated a positive linear relationship between $\Delta Pes/\Delta t_{PRE}$ and $\Delta Pga/\Delta t_{PRE}$, mean correlation coefficient of, 0 89 ± 0 10 Patients presented with varying Pdi ratios, range 0 97 (P6) to 6 84 (P3)

9.9 Analysis of the Initial Phase of Pressure Generation (from 0 to Peak Inspiratory Flow Acceleration)

A combined four parameter graph is presented in **Figure 9 7** For each of the four relationships presented, the regression lines for the relationships of each individual subject are displayed In the upper right quadrant, Dyspnea is plotted versus $\Delta Pes/P_{cap}$ The lower right quadrant plots $\Delta Pes/P_{cap}$ versus rate of change of pleural pressure, measured from the onset of inspiratory flow to the peak of the inspiratory flow acceleration ($\Delta Pes/\Delta t$), measured in cmH20/second The upper left quadrant plots Dyspnea versus the rate of change of gastric pressure with respect to time, again from the onset of inspiratory flow to the peak of inspiratory flow acceleration ($\Delta Pga/\Delta t$), measured in cmH20/second The lower left quadrant plots $\Delta Pes/\Delta t$ versus $\Delta Pga/\Delta t$ For each individual subject, numerical values for each of the four variables at quiet breathing and at maximum exercise are presented in **Table 9 4**

9.9.1 Dyspnea versus $\Delta Pes/P_{cap}$ [fig 9 7, upper right]

This relationship has been previously discussed (section **9.7 2**) It is re-plotted in order to compare its results to other investigated parameters

9.9.2 $\Delta Pes/\Delta t$ versus $\Delta Pes/P_{cap}$ [fig 9 7, lower right]

The relationship of $\Delta Pes/\Delta t$ to $\Delta Pes/P_{cap}$ expressed in percentage indicates, for a given 1% increase in the amount of pleural pressure being generated, expressed in relationship to the maximum pressure generating capacity available, what is the change in the velocity of the pleural pressure swing from 0 inspiratory flow to peak inspiratory flow acceleration.

All subjects demonstrated strong relationships between $\Delta Pes/\Delta t$ and $\Delta Pes/P_{cap}$,

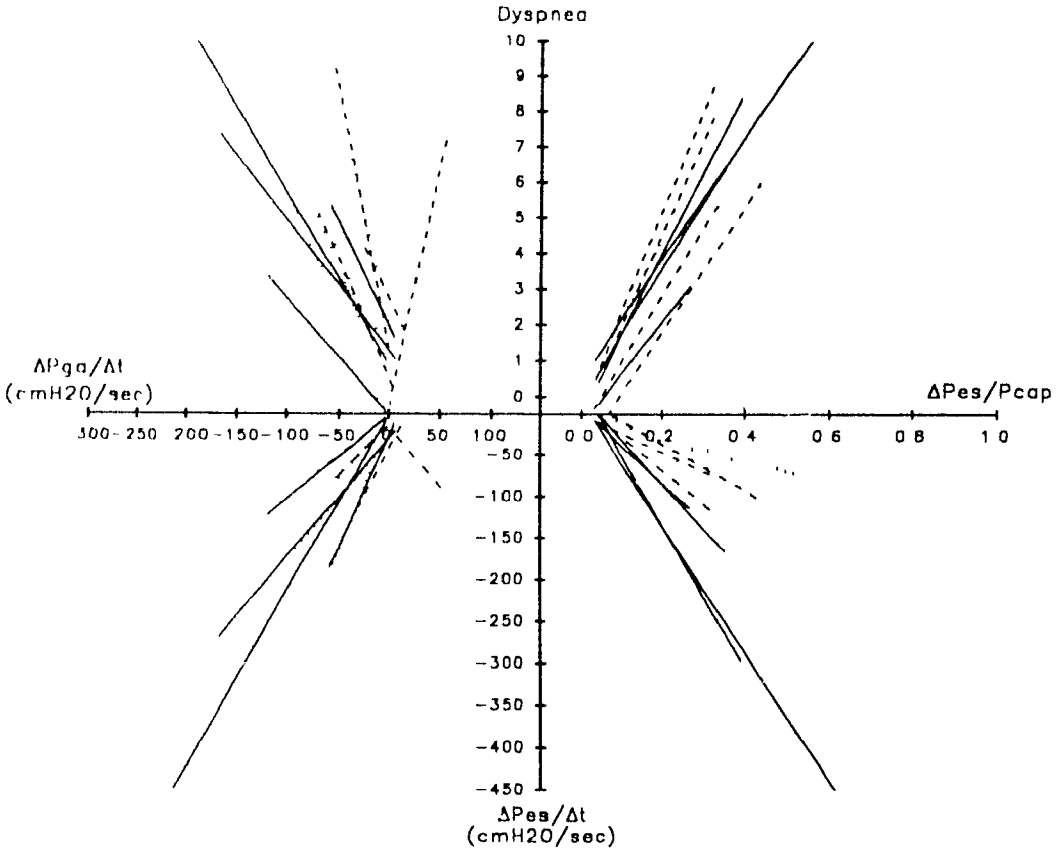


Figure 9 7 Lines plotted represent the linear regression for each individual subject for each of the four presented relationships Solid lines (———) represent athletes, dashed lines (- - - - -) represent normal subjects and dotted lines ( ) represent COPD patients. See text for a detailed description of each plot.

SUBJECT	QB Dyspnea	MAX Dyspnea	QB ΔPes/Pcap mean ±sd	MAX ΔPes/Pcap mean ±sd	QB ΔPes/Δt (cmH20/sec) mean ±sd	MAX ΔPes/Δt (cmH20/sec) mean ±sd	QB ΔPga/Δt (cmH20/sec) mean ±sd	MAX ΔPga/Δt (cmH20/sec) mean ±sd
A1	0	9 5	0 03 ±0 01	0 64 ±0 05	-9 86 ± 3 95	-423 95 ±66 40	-3 03 ± 0 79	-212 00 ±41 34
A2	0	4 0	0 07 ±0 02	0 27 ±0 02	-3 67 ± 1 16	-123 38 ±14 33	-3 36 ± 0 90	-119 19 ±19 69
A3	0	6 0	0 03 ±0 00	0 33 ±0 04	-5 58 ± 1 86	-213 20 ±40 3	-2 76 ± 0 96	-23 44 ±57 16
A4	0	7 0	0 05 ±0 01	0 39 ±0 07	-8 98 ± 3 90	-293 85 ±54 46	6 51 ± 5 39	-151 44 ±31 34
N1	0	9 0	0 04 ±0 01	0 32 ±0 06	-11 28 ±10 14	-71 86 ±23 75	-2 41 ±16 42	-56 15 ±19 35
N2	0	8 0	0 04 ±0 01	0 32 ±0 02	-6 93 ± 2 92	-166 02 ±37 73	0 32 ± 2 30	-29 70 ±24 13
N3	0	5 0	0 03 ±0 00	0 34 ±0 03	-6 18 ± 1 13	-83 84 ±45 36	4 03 ± 2 14	-69 11 ±38 17
N4	0	8 0	0 05 ±0 00	0 51 ±0 09	-4 70 ± 0 43	-86 75 ±27 42	5 90 ± 0 60	56 23 ±39 36
P1	0	7 0	0 21 ±0 04	0 74 ±0 08	-18 54 ± 5 53	-150 95 ±25 97	6 55 ± 2 09	-95 04 ±30 30
P2	0	7 0	0 20 ±0 02	1 01 ±0 11	-23 92 ± 3 15	-167 21 ±30 23	-5 30 ± 2 50	-109 45 ±11 58
P3	0	5 0	0 38 ±0 05	0 59 ±0 12	-109 62 ±30 59	-165 70 ±29 57	-12 2 ±14 17	-48 62 ±24 87
P4	1 0	5 0	0 20 ±0 02	0 80 ±0 06	-28 78 ±12 71	-200 00 ±43 82	-9 20 ± 6 09	-59 73 ±36 75
P5	1 0	5 0	0 22 ±0 04	0 59 ±0 05	-34 62 ± 6 09	-81 64 ±11 39	-20 59 ± 4 48	-59 28 ± 3 69
P6	2 0	9 0	0 09 ±0 02	0 34 ±0 05	-12 64 ± 5 89	-72 67 ±17 55	0 02 ± 2 01	-39 91 ±14 60
P7	2 0	4 0	0 17 ±0 02	0 37 ±0 02	-30 23 ± 5 72	-92 12 ±20 93	-1 92 ± 2 51	-50 19 ± 8 75

Table 9.4

mean group correlation coefficients of 0 97 ±0 03, 0.91 ± 0 03, 0 96 ±0 01 for the athletic, normal and patient groups respectively

9 9 2 1 The ΔPes/Δt to ΔPes/Pcap Relationship in Athletes

All athletes presented with similar, high (ΔPes/Δt) / (ΔPes/Pcap X 100) relationships with a mean value of -6 51 ± 1 86 cmH20/sec/1%

9.9.2.2 The ΔPes/Δt to ΔPes/Pcap Relationship in Normals

The normal group presented with a mean relationship that was significantly lower than the athletic group, mean of -2 98 ± 0 76 cmH20/sec/1%, p<0 05

9.9 2 3 The ΔPes/Δt to ΔPes/Pcap Relationship in Patients

The patient group presented with similar mean values as the normal group; however significantly lower than the athletic group -2 28 ± 0 60 cmH20/sec/1%, p<0 05

9.9.3 Dyspnea versus ΔPga/Δt [fig 9 7, upper left]

Three of the four athletes (A1,A2,A3) presented with a mean ΔPga/Δt of -3.05 ±0 30 cmH20/sec at quiet breathing The remaining athlete (A4) presented with a positive mean ΔPga/Δt at rest of 6 51 cmH20/sec

One normal subject (N1) demonstrated a negative mean ΔPga/Δt of -2.41 cmH20/sec at quiet breathing The remaining three normals (N2,N3,N4) demonstrated positive mean ΔPga/Δt at rest, ranging from 0 32 cmH20/sec to 5 90 cmH20/sec

Five of the seven patients (P2,P3,P4,P5,P7) demonstrated negative mean ΔPga/Δt at quiet breathing, ranging from -1 92 cmH20/sec (P7) to -20 59 cmH20/sec (P5) The remaining two patients (P1,P6) presented with positive mean ΔPga/Δt at rest of 6.55 cmH20/sec and 0 02 cmH20/sec respectively Addressing the variability of patient mean values, P3, P4 and P6 each presented with large variances about their individual means **[Table 9.4]**

At maximum exercise, two of the four athletes (A1,A4) presented with very rapid negative ΔPga/Δt of -212 0 cmH20/sec (A1) & -151.44 cmH20/sec (A4) A2, who only

reached 80% of his maximum exercise also presented with a fast negative ΔPga/Δt of -119 19 cmH20/sec Even though A3 demonstrated a small negative mean value of -23 44, the standard deviation was ±57 16 cmH20/sec This allows the inference that for some breaths he demonstrated negative gastric swings, sometimes there was no change in gastric pressure and sometimes a slightly positive gastric swing existed Three of the four normals (N1,N2,N3) demonstrated a negative mean ΔPga/Δt at maximum exercise of -51 65 ±20 08 cmH20/sec, significantly slower than athletes A1,A2,A3 The remaining normal (N4) presented with a positive Pga/Δt at maximum exercise of +56 23 cmH20/sec All normal subjects presented with large variances about their individual mean values **[Table 9.4]**

All patients demonstrated similar negative mean ΔPga/Δt at maximum exercise, -66 03 ±25 98 cmH20/sec At the individual patient level, four of the patients (P1,P3,P4,P6) demonstrated large variances about their individual mean ΔPga/Δt **[Table 9 4]**

9.9.3.1 Dyspnea Response to ΔPga/Δt of Athletes

Three of the four athletes (A1,A2,A4) demonstrated a strong correlation between dyspnea and ΔPga/Δt, mean correlation coefficient of 0 93 ±0 06 A3 presented with a poor correlation coefficient of 0 40 As a group the athletes presented with a mean dyspnea response to ΔPga/Δt of -0 04 ±0 01

9.9.3.2 Dyspnea Response to ΔPga/Δt of Normals

Three of the four normals, N1,N3,N4 demonstrated a strong correlation between dyspnea and ΔPga/Δt, mean correlation coefficient of 0 87 ±0 06 The correlation for N2 was insignificant Within the normal group, each individual subject presented with a very different dyspnea response to ΔPga/Δt N1 presented with a high dyspnea response, when compared to the athletes, of -0 14 N3 presented with a low dyspnea response, similar to the athletes, -0 06, and N4 presented with a positive dyspnea response of 0 14

9.9.3.3 Dyspnea Response to ΔPga/Δt of Patients

All patients demonstrated a strong correlation between dyspnea and ΔPga/Δt, mean

correlation coefficient of 0 89 ± 0 09 Low responding patients (P1,P2,P4,P5,P7) demonstrated a similar mean dyspnea response to ΔPga/Δt when compared to the athletes, -0 07 ± 0 02, p>0 05 High dyspnea responding patients (P3,P6) demonstrated significantly higher mean dyspnea responses when compared to both the athletic group and the low responding patient group, -0 13 ± 0 02, p<0 05

9 9 4 The Relationship of ΔPes/Δt to ΔPga/Δt [fig 9.7, lower left]

The relationship of ΔPes/Δt to ΔPga/Δt indicates the contribution of the rate of the gastric pressure swing to the rate of the pleural pressure swing (Pdi ratio) A ratio of 1 indicates that for every change in the rate of the gastric pressure swing, an equal and similar directional change in the rate of the pleural pressure swing occurred (Pdi = 0), whereas a ratio of -1 indicates that a large Pdi is being generated

9.9.4 1 ΔPes/Δt to ΔPga/Δt Relationship of Athletes

Three athletes (A1,A2,A4) demonstrated a positive relationship between ΔPes/Δt and ΔPga/Δt, mean correlation coefficient of 0 97 ± 0 02 A weaker relationship was demonstrated by A3, correlation coefficient of 0 64 As a group, the athletes presented with a mean value of ΔPes/Δt / ΔPga/Δt of 1 81 ± 0.74

9.9.4.2 ΔPes/Δt to ΔPga/Δt Relationship of Normals

Two normals (N1,N3) demonstrated a much strong relationship between ΔPes/Δt and ΔPga/Δt than either N2 or N4 As a group, the normal subjects had a mean correlation coefficient of 0 73 ± 0 22 N1, N2 and N3 demonstrated Pdi ratio values of 1.22, 2 30 and 0 99, while N4 presented with a negative ratio of -1 14

9 9 4 3 ΔPes/Δt to ΔPga/Δt Relationship of Patients

All patients demonstrated a strong linear relationship between ΔPes/Δt and ΔPga/Δt, mean correlation coefficient of 0 94 ± 0 08 The patient presenting the weakest correlation was P3, correlation coefficient of 0 77 All patients demonstrated similar ratios when

compared to the both the athletic group and the three normals presenting with positive Pdi ratios (N1,N2,N3), mean patient Pdi ratio of 1.61 ±0 65, p>0 05

9.10 The Pressure-Time Index of the Inspiratory Muscles

The relationship between the duty cycle measured from pressure (Ti/Ttot) **[fig 8 2b]** and $\Delta\overline{Pes}/Pcap$ is plotted **(fig 9 8 a)** Symbol and line definitions are presented in **Table 9.5.** Mean values at quiet breathing and at maximum exercise are plotted for each individual subject Since the product of $\Delta\overline{Pes}/Pcap$ and pressure Ti/Ttot represents the pressure-time index of the inspiratory muscles (TTim), iso-TTim lines were calculated and plotted, TTims of 0 10, 0 15, 0 20, 0 25

9.10.1 Pressure Duty Cycle (Ti/Ttot)

The athletic, normal and patient groups presented with similar mean pressure derived Ti/Ttot values at quiet breathing, 0 38 ±0 06, 0 42 ±0 07 and 0 38 ±0 07, p>0 05

At maximum exercise, athletes and normals presented with similar mean Ti/Ttot, 0.55 ± 0 05 and 0 57 ± 0 04 The patient group had significantly lower mean Ti/Ttot when compared to both the athletic and normal group, 0 40 ±0 07, p<0 05

9.10.2 $\Delta\overline{Pes}/Pcap$

Athletes and normals presented with similar mean $\Delta\overline{Pes}/Pcap$ at quiet breathing, 0.03 ±0 01 and 0 02 ±0 00; however patients' mean $\Delta\overline{Pes}/Pcap$ at quiet breathing was significantly higher, 0 14 ±0 06, p<0 05

At maximum exercise, the mean $\Delta\overline{Pes}/Pcap$ was not statistically different between the athletic, normal and patient groups, 0 32 ±0 12, 0 26 ±0 05, 0 45 ±0 18 Looking at individual subjects within the groups, A1 presented with a very high $\Delta\overline{Pes}/Pcap$ of 0 46, resulting in the large standard deviation observed about the mean of the athletic group Individual patients also presented with widely varying values of $\Delta\overline{Pes}/Pcap$ at maximum exercise P1,P2,P4 (all low responding patients) presented with higher $\Delta\overline{Pes}/Pcap$ values, when compared to the remaining patients, athletes and normals, mean $\Delta\overline{Pes}/Pcap$ of 0 62 ±0 09 P3,P5,P6,P7 presented with similar mean $\Delta Pes/Pcap$ when compared to the

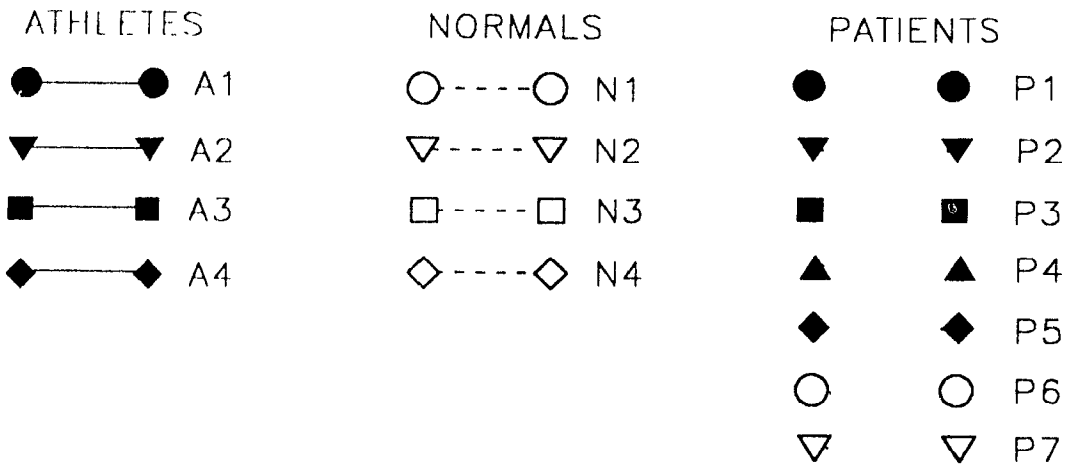

ATHLETES
A1
A2
A3
A4
NORMALS
N1
N2
N3
N4
PATIENTS
P1
P2
P3
P4
P5
P6
P7

Table 9.5

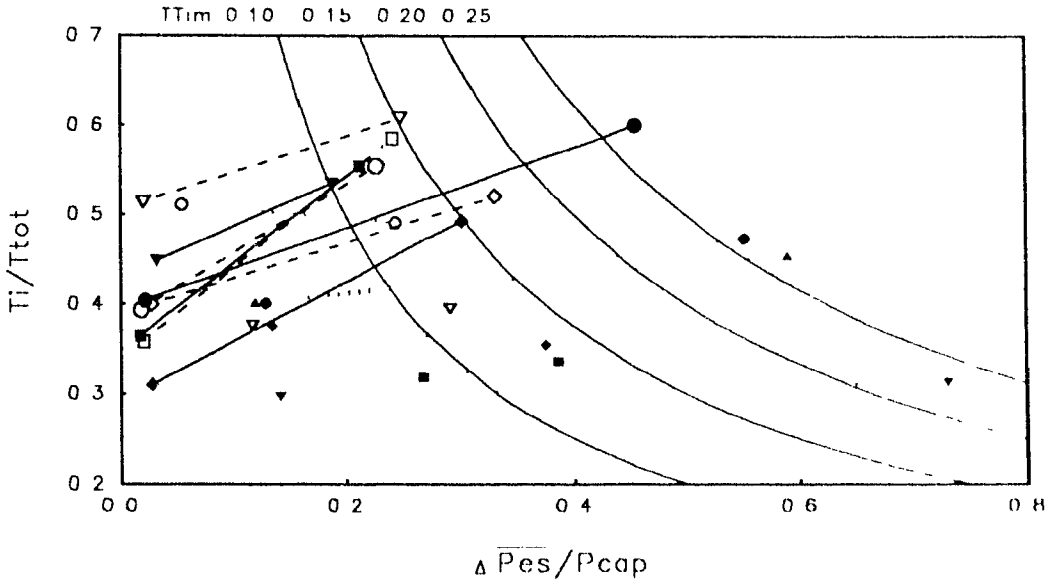


Figure 9 8.a Ti/Ttot is plotted versus ΔPes/Pcap Points represent values at quiet breathing and maximum exercise for each subject See text for details

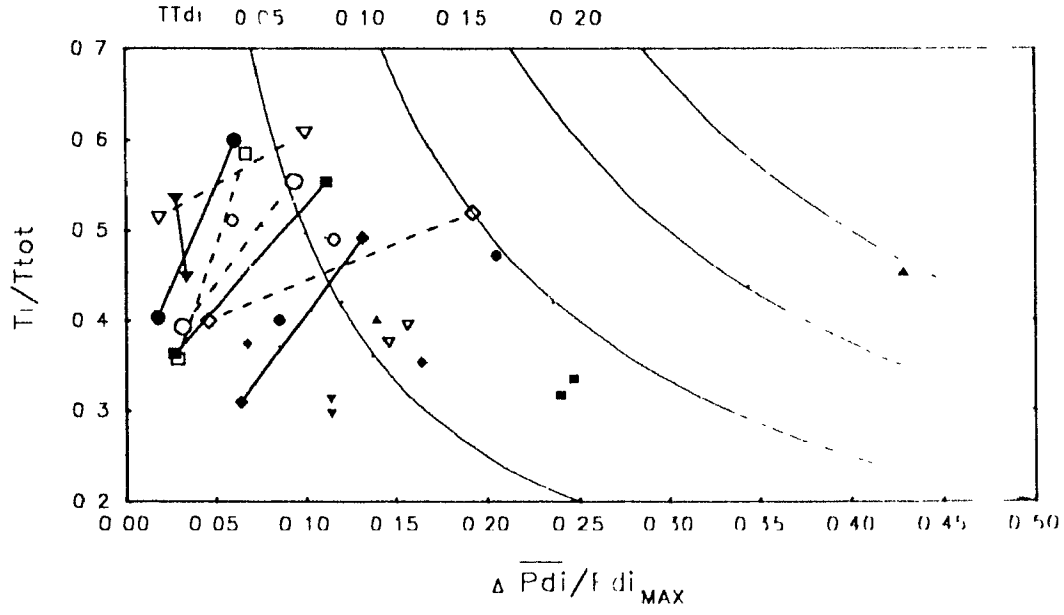


Figure 9.8 b Ti/Ttot is plotted versus $\Delta Pdi/Pdi_{MAX}$ Points represent values at quiet breathing and at maximum exercise for each subject See text for details

athletes and normals, 0 32 ±0 07

9 10 3 TTim

At quiet breathing, the athletic and normal groups presented with similar mean TTim, 0 01 ±0 00 and 0 01 ±0 00 The patient group presented with significantly higher mean TTim at quiet breathing compared to both athletes and normals, 0 05 ±0.02, $p<0\ 05$. At maximum exercise, no significant difference existed between the mean TTim values achieved by the athletic group, 0 16 ±0 08, normal group, 0 15 ±0 02, or patient group, 0 18 ±0 07, $p>0\ 05$

Within groups, A1 achieved a much higher mean TTim of 0 27 when compared to the remaining athletes This resulted in the observed large standard deviation about the athletic group mean A3 and A4 achieved similar maximum TTim when compared to the group of normal subjects, 0 13 and 0 15 Patients again demonstrated a large variance in maximum achieved TTim P1,P2,P4 (all low responders) achieved higher TTims of 0.26, 0 23, 0 27, when compared to the remaining patients Their TTim resembled that of A1 P3,P5,P6,P7 reached similar levels of TTim to the remaining athletes A2,A3,A4 and all normal subjects, mean TTim of 0 12 ±0 01

9.11 The Pressure-Time Index of the Diaphragm

The relationship between the pressure duty cycle (Ti/Ttot) and $\Delta\overline{Pdi}/Pdi_{max}$ is plotted **(fig 9 8 b)** Please see **Table 9 5** for definitions of symbols and lines Mean values at quiet breathing and at maximum exercise are plotted for each individual subject Given that the pressure-time index of the diaphragm (TTdi) is the product of Ti/Ttot and $\Delta\overline{Pdi}/Pdi_{max}$, iso-TTdi lines were calculated and also plotted (continuous curving lines of TTdi = 0.05, 0 10, 0 15, 0 20) Each iso-TTdi line represents all combinations of $\Delta\overline{Pdi}/Pdi_{max}$ X Ti/Ttot that produce that given TTdi

9.11 1 Pressure Duty Cycle (Ti/Ttot)

The same Ti/Ttot used in the above TTim analysis were also utilized for the plotting

of the TTdi relationship

9.11.2 $\Delta\overline{PdT}/Pdi_{max}$

At quiet breathing, the athletic and normal groups demonstrated similar mean $\Delta\overline{PdT}/Pdi_{max}$, 0 04 ±0 02 and 0 03 ±0 01 while the patient group presented with significantly higher mean $\Delta\overline{PdT}/Pdi_{max}$ at quiet breathing, 0 12 ±0 06 P3 presented with an extremely high $\Delta\overline{PdT}/Pdi_{max}$ at quiet breathing, 0 24 At maximum exercise, no significant difference existed between the mean group values of the athletes, normals and patients Within specific groups, there was considerable variability in the $\Delta\overline{PdT}/Pdi_{max}$ achieved at maximum exercise A3,A4,N1,N2 presented with similar mean $\Delta\overline{PdT}/Pdi_{max}$, 0 11 ±0 02 A1 and N3 presented with similar lower $\Delta\overline{PdT}/Pdi_{max}$ of 0 06 and 0.07 at maximum exercise N4 presented with a high $\Delta\overline{PdT}/Pdi_{max}$ of 0 19 Within the patient group a large variation existed between individual subjects P2 and P6 (both low responders) presented with similar mean $\Delta\overline{PdT}/Pdi_{max}$ as A3,A4,N1,N2, of 0 11 (P2) and 0 12 (P6) At the opposite extreme, P4 demonstrated a mean $\Delta\overline{PdT}/Pdi_{max}$ of 0 43 at maximum exercise

9.11.3 TTdi

At quiet breathing, the athletic and normal groups demonstrated similar mean TTdi's of 0 01 ±0 01 and 0 01 ±0 00 The patient group demonstrated significantly higher mean TTdi at quiet breathing, 0 04 ±0 02, $p<0\ 05$ At maximum exercise, the athletic, normal and patient groups demonstrated similar mean TTdi's, 0 05 ±0 01, 0 06 ±0 03 and 0 08 ±0 05 respectively.

Individual subjects within each group demonstrated varying mean TTdi's at maximum exercise A1 and N3 both presented with the lowest TTdi's at maximum exercise, measured at 0 04 Individual patients also demonstrated a wide range of TTdi values For example, P2 achieved only a maximum TTdi of 0 04 whereas P4 achieved a maximum TTdi of 0 20, in excess of the fatigue threshold of 0 15

9 12 The Relationship of Dyspnea to TTim and TTdi

The relationship of dyspnea to TTim and TTdi is plotted in a combined graph in **fig 9.9**. Please see **Table 9 5** for definitions of symbols and lines On the left graph, Dyspnea is plotted versus TTdi The right side of the graph represents the relationship between Dyspnea and TTim Mean values are plotted for individual subjects at quiet breathing and at maximum exercise The Δdyspnea (the change between quiet breathing and maximum exercise) response to Δ changes from quiet breathing to maximum of TTim and TTdi are examined

9 12.1 Dyspnea versus TTim [fig 9 9 right]

9.12.1.1 ΔDyspnea Response to ΔTTim of Athletes

Athletes presented with similar Δdyspnea responses to ΔTTim, group mean of 46.56 ± 7 81, with a range of individual subject values between 35.74 (A1) to 53 92 (A3).

9.12 1.2 ΔDyspnea Response to ΔTTim of Normals

The mean Δdyspnea response to TTim of the normal group was not statistically different from the athletes, 54 67 ± 16.17, p>0 05 Within the normal group, a large variability existed with a range of mean Δdyspnea responses between 36 88 (N3) to 75 59 (N1)

9.12.1.3 ΔDyspnea Response to ΔTTim of Patients

As a group, patients presented with a similar Δdyspnea responses to ΔTTim when compared to the athletes and normals, 50.37 ± 32 40, p>0.05. When the responses are grouped into the previously defined "low responding" patients (P1,P2,P4,P5,P7) v "high responding" patients (P3,P6) a differences did exist Low responding patients demonstrated much lower Δdyspnea responses to TTim, 33 19 ± 11 34, when compared to high responding patients 93 30 ± 24 99, p<0 05 The Δdyspnea responses of the low responding patients were similar to that of A1 and N3 whereas the high responding patients demonstrated similar responses to N1 and N2

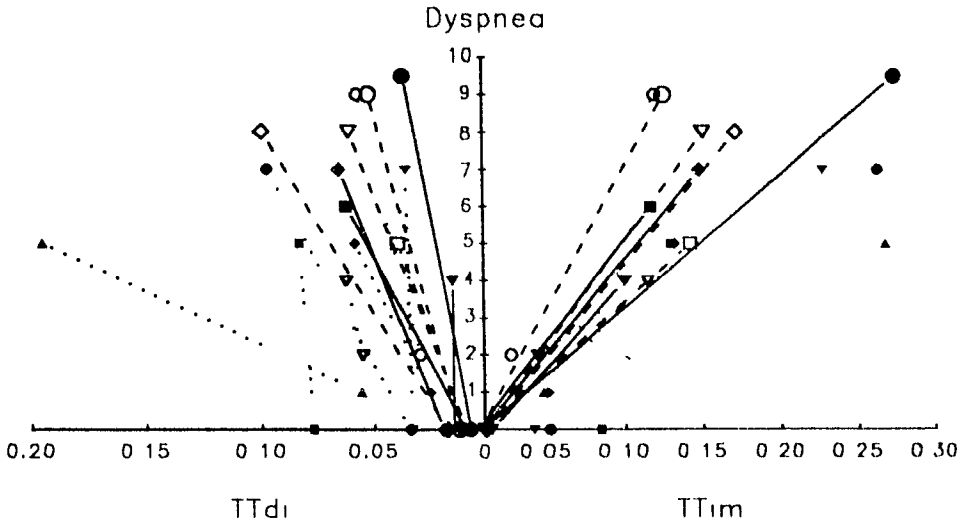


Figure 9.9 Dyspnea is plotted versus TTdi and TTim Points represent values at quiet breathing and maximum exercise for each individual subject. See text for description.

9.12.2 Dyspnea versus TTdi [fig 9.9 left]

9.12.2.1 ΔDyspnea Response to ΔTTdi of Athletes

The athletic subjects demonstrated a wide variation in Δdyspnea responses to ΔTTdi Two athletes (A1,A2) presented with very high Δdyspnea responses (324.61 and 8620 00) This was due to the fact that TTdi had increased very little at maximum exercise from that measured at quiet breathing The remaining two athletes (A3,A4) presented with Δdyspnea responses to TTdi of 11[illegible]29 and 155 3

9.12 2 2 ΔDyspnea Response to ΔTTdi of Normals

The mean Δdyspnea response to ΔTTdi of normals was 164.84 ±53 98, similar to A3,A4 but much lower than that of A1 and A2

9.12.2.3 ΔDyspnea Response to ΔTTdi of Patients

A large variance in Δdyspnea responses to ΔTTdi also existed within the patient group In general, P2 and P3 exhibited very small increases in TTdi when maximum exercise was compared to quiet breathing, thus their Δdyspnea responses were very high (4046 24 and 761 14), similar to A1 and A2 The remaining patients presented with maximum dyspnea responses ranging from 28.68 (P4) to 281 69 (P7).

9.13 Comparison of the ΔDyspnea Response to ΔTTim versus ΔTTdi

Comparing individual subject's Δdyspnea response to ΔTTim versus ΔTTdi, some general observations can be made The two athletes with the lowest Δdyspnea response to ΔTTim (A1,A2) presented with the largest Δdyspnea response to ΔTTdi. N3 who presented with a low Δdyspnea response to ΔTTim also presented with a reasonably high Δdyspnea response to ΔTTdi In the patient group, P1,P2,P5 and P7 (all defined low dyspnea responders) each presented with a low Δdyspnea response to ΔTTim and yet high Δdyspnea response to ΔTTdi In contrast, both patients termed high responders (P3,P6) demonstrated a high Δdyspnea response to both ΔTTdi and ΔTTim Conversely, P4, a low responder, exhibited a low Δdyspnea response to both ΔTTim and ΔTTdi

9.14 The Mechanics of Breathing: A Qualitative Analysis

Muscular coordination and breathing mechanics are qualitatively evaluated through the use of both Macklem diagrams, plotting Pes versus Pga, and Konno Mead diagrams, plotting rib cage versus abdominal wall movement (RC versus AB). Representative examples of the observed breathing patterns during exercise at an iso-dyspnea level of 5 will be presented for the athletes, normals and patients. Iso dyspnea is defined as the same numerical value of dyspnea, thus an iso-dyspnea level of 5 was chosen to permit a standardized comparison between subjects. All subjects experienced this level of dyspnea at some point in time during their progressive exercise test.

The following analysis expands upon the concept of "low responding" and "high responding" subjects. This is based upon the already observed differences in the response of dyspnea to changes in pleural pressure (ΔPes/Pcap) of individual subjects **(see 9.7.2)**.

This analysis addresses the question of whether breathing coordination and mechanics are explanatory mechanisms for observed variations in the dyspnea response of low responders versus high responders.

In order to qualitatively assess and compare mechanics and coordination between subjects, standardized timing is presented on all graphics. The definitions of all timing symbols and lines used on all of the following graphics is detailed in **Table 9.6**. This method of analysis will be used throughout the remainder of the results section unless otherwise specified. It should also be noted that the units of measurement for both RC and AB displacement are referred to as "Arbitrary Units" on all graphics. This is not meant to indicate that changes in RC and AB excursions presented are not quantitatively equivalent. Delta changes in amplitude are equal in unit measurement. The units of measurement, however at individual data points cannot be compared. For example, a 2 on the RC axis does not necessarily correspond to a 2 on the AB axis. A negative baseline value does not necessarily indicate a change in compartmental EEV compared to rest. Rather if a change downward is seen in the baseline value from one breath to another, this would represent a decrease in compartmental EEV.

Definitions of Symbols Used in the Qualitative Analysis

■ The onset of the negative inspiratory pressure swing (0 sec)

● 5 % of the Ttot of that individual breath

○ 10% of the Ttot of that individual breath

△ 25% of the Ttot of that individual breath

□ The end of inspiratory flow (ie. the end of inspiration)

Definitions of Lines Used in the Qualitative Analysis

Macklem Diagrams

Solid Line ( ) represents a Pes of 0 cmH20

Dashed Line (----------) represents an iso Pdi =0 line

Konno-Mead Diagrams

Dashed Line (----------) represents an isovolume line

Table 9.6

9.14.1 Mechanics of Breathing of Athletes versus Normal Subjects

All athletes have previously been defined as low dyspnea responders to ΔPes/Pcap Meanwhile, in the normal group, 2 subjects (N3,N4) presented with a low dyspnea response to ΔPes/Pcap and two normals (N1,N2) presented with a high dyspnea response to increases in ΔPes/Pcap

9.14.1.1 Low Responding Athletes versus High Responding Normals

Macklem diagrams (Pes v Pga) are presented for a representative breath of a low responding athlete (A1) **[fig 9 10 a]** and high responding normal (N1) **[fig 9 11 a]** The corresponding inspiratory flows, Pes and Pga swings are also individually plotted as a function of time for the same breath for both A1 **[fig 9 10 b]** and N1 **[fig 9 11 b]** The Konno-Mead diagrams (RC v AB) for the same breath of A1 and N1 are presented in **fig 9.10 c** and **fig 9 11 c** respectively The corresponding RC and AB displacements as a function of time are individually plotted for A1 **[fig 9.10 d]** and N1 **[fig 9.11 d]** respectively

Comparing the Macklem diagrams of A1 **[fig 9 10.a]** and N1 **[fig 9 11 a]**, it is observed that the athletic subject begins breathing from a much higher, positive end expiratory pleural pressure (EEP) when compared to the normal subject However, within 5% of the total breath time, the athlete has achieved a large negative Pes swing, coinciding with a large negative Pga swing Pes has reached 0 cmH20, whereby inspiratory flow begins In contrast, the high responding normal has only achieved a very small negative pleural and gastric pressure swing in the first 5% of Ttot Within 10% of the Ttot, the athlete has achieved peak negative Pes, peak negative Pga and reached peak inspiratory flow **[fig 9.10.b]** In contrast, the normal subject has only achieved a small portion of his maximum negative Pes swing, relatively no change in Pga has occurred and inspiratory flow is still accelerating **[fig 9 11 b]** The athlete, at 25% of Ttot, demonstrates both Pes and Pga which are relatively unchanged from their peak negative values and the maintenance of a constant peak inspiratory flow In contrast, the normal, is still generating a negative Pes swing, ΔPga is relatively unchanged and inspiratory flow has just now reached its maximum value From 25% Ttot to the end of inspiration, the athlete demonstrates both Pes and Pga swings in the positive direction, whereas the normal subject demonstrates a large positive

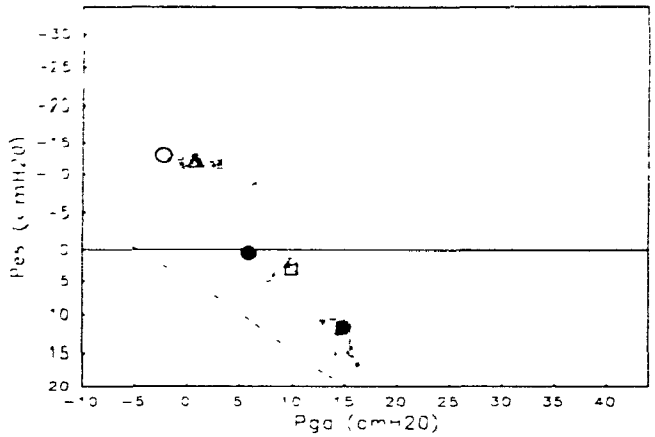


Figure 9.10 a Mackem Diagram for low responding athlete (A1) Pes is plotted versus Pga

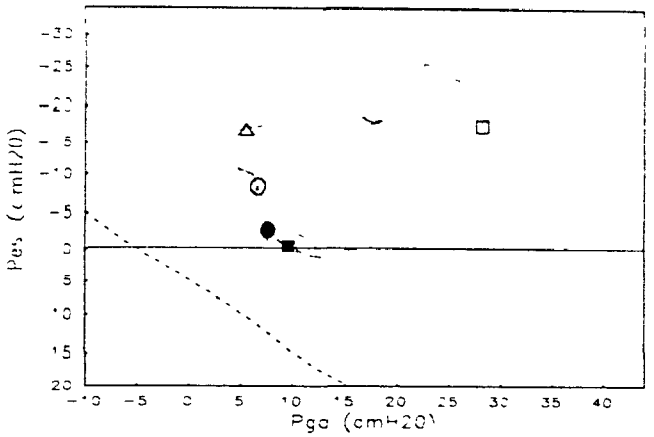


Figure 9.11 a Mackem diagram for a high responding normal (N1) Pes is plotted versus Pga

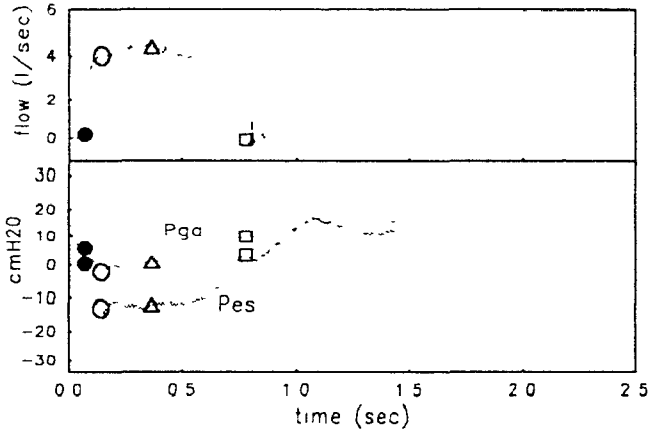


Figure 9.10 b Inspiratory flow, Pes and Pga are individually plotted versus time for A1

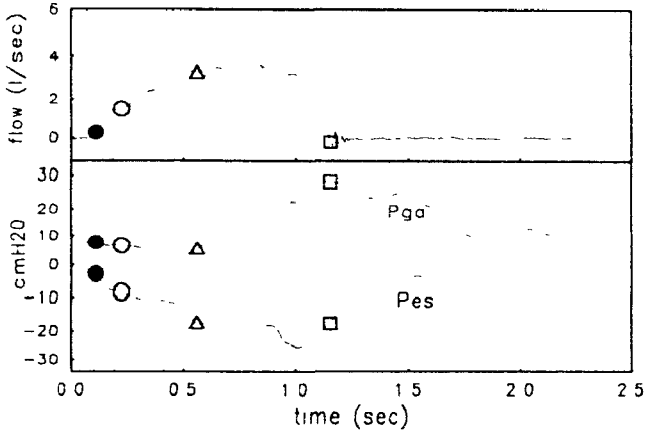


Figure 9.11 b Inspiratory flow, Pes and Pga are individually plotted versus time for N1

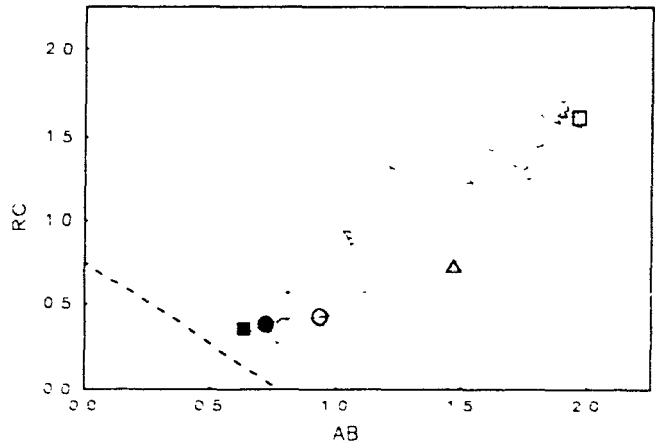


Figure 9.10 c Konno–Mead diagram for A1 RC displacement is plotted v AB displacement All units are arbitrary

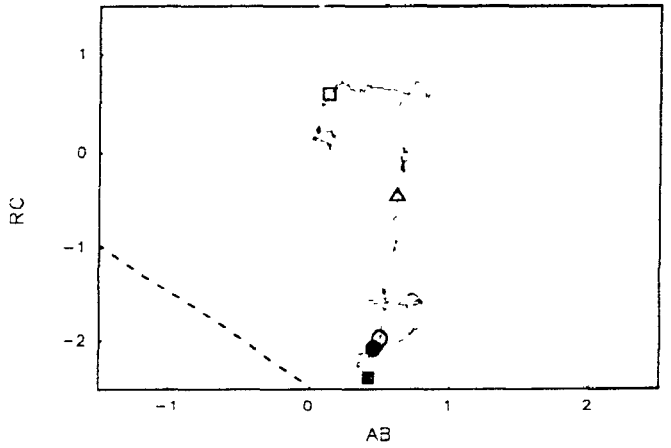


Figure 9.11 c Konno–Mead diagram for N1 RC displacement is plotted v AB displacement All units are arbitrary

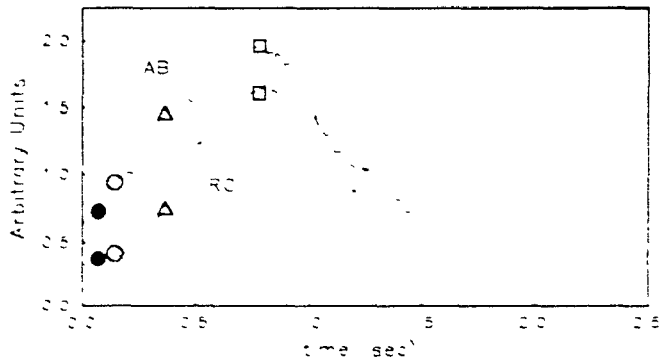


Figure 9.10 c RC and AB displacement are plotted versus time for A1

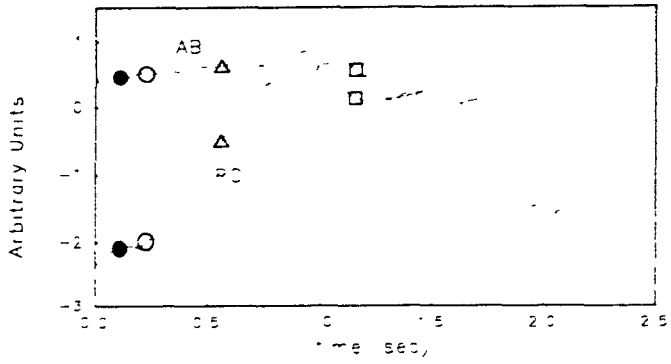


Figure 9.11 c RC and AB displacement are plotted versus time for N1

ΔPga and a much smaller positive ΔPes

Analysis of the corresponding Konno-Mead diagram **[fig 9.10.c]** and separate RC and AB displacements v time plot **[fig 9 10 d]** for A1, demonstrates a predominantly AB pattern of breathing In contrast, N1, **[fig 9.11 c]**, **[fig 9 11.d]** presents with a predominantly RC pattern of breathing Comparing the timing of RC and AB displacement, within the first 5% and 10% of Ttot, A1 demonstrates a large outward abdominal displacement coinciding with very little outward RC movement, whereas N1 presents with both relatively small outward RC and AB movement From 10% to 25% Ttot, A1 demonstrates similar RC and AB expansion, whereas N1 demonstrates large RC displacement with very little AB expansion From 25% Ttot to the end of inspiration, RC and AB displacement is still increasing for A1 and maximum displacement is achieved at end inspiration In contrast, the normal subject is still exhibiting a predominant pattern of RC expansion and the AB actually begins to move inwards prior to the end of inspiration

9 14.1 2 Low Responding Athlete versus Low Responding Normal

Macklem diagrams (Pes v Pga) are presented for a representative breath of a low responding athlete (A4) **[fig 9 12 a]** and a low responding normal (N4) **[fig 9.13 a]** The corresponding inspiratory flows, Pes and Pga swings are individually presented as a function of time for A4 **[fig 9 12 b]** and N4 **[fig 9. 13 b]** The Konno-Mead diagrams (RC v AB) for the same breaths of A4 and N4 are presented in **fig 9 12 c** and **fig 9.13.c** respectively In addition, individual RC and AB displacements versus time for A4 **[fig 9 12.d]** and N4 **[fig 9 13 d]** are presented

Comparing the Macklem diagrams of A4 **[fig 9 12.a]** and N4 **[9 13 a]**, it is observed that both subjects begin breathing from similar positive end pleural pressures (EEP) Within 5% of Ttot, A4 has achieved a large negative pleural pressure swing, corresponding to a negative gastric pressure swing and inspiratory flow has almost reached its peak value N4 presents with a very rapid negative pleural pressure swing, reaching 0 cmH20, however, no change in Pga is observed (ΔPga =0) Inspiratory flow has just begun Within 10% of the Ttot, A4 has almost reached peak negative Pes, peak negative Pga and peak inspiratory flow **[fig 9 12.b]** Comparing N4 **[fig 9 13 b]**, despite peak inspiratory flow being maximum,

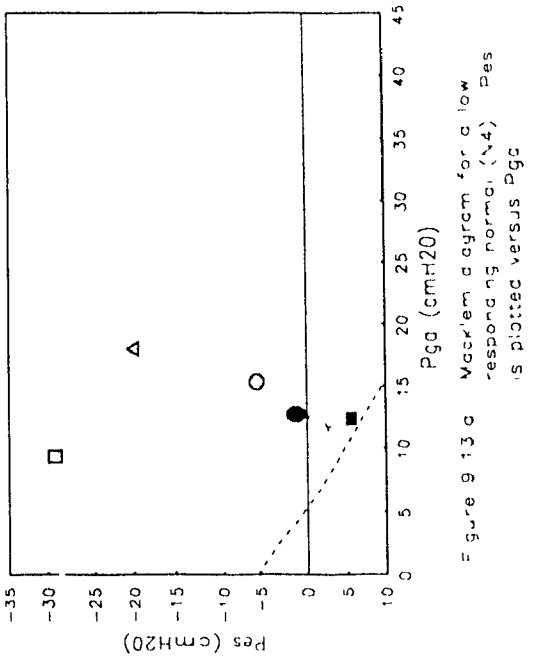


Figure 9.13 a Wasserman diagram for a low responding normal (A4) Pes is plotted versus Pga

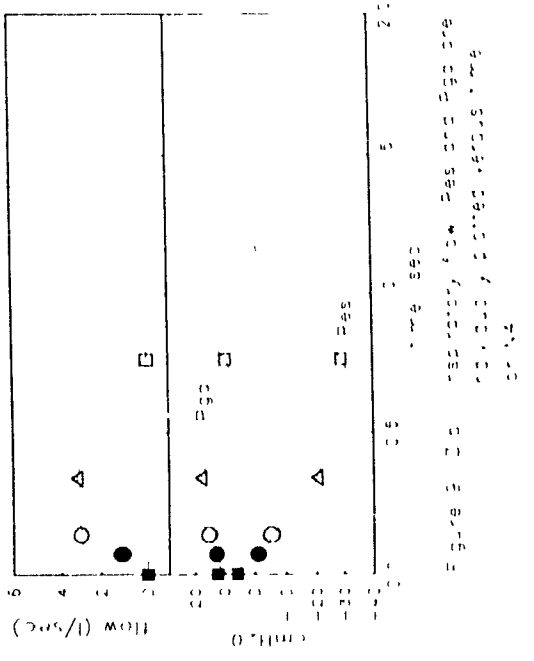


Figure 9.13 b Respiratory flow, Pes and Pga are plotted versus time

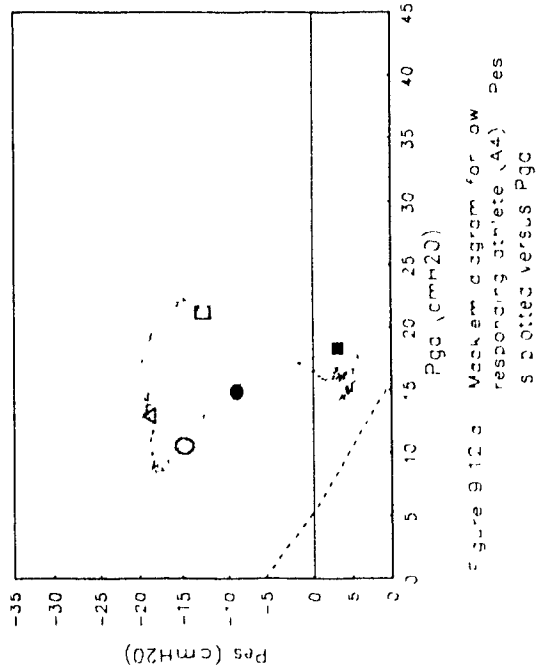


Figure 9.12 a Wasserman diagram for a low responding athlete (A4) Pes is plotted versus Pga

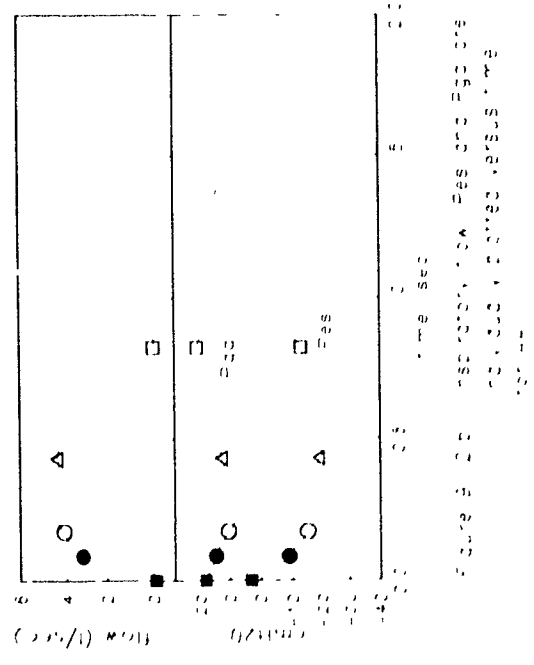


Figure 9.12 b Respiratory flow, Pes and Pga are plotted versus time

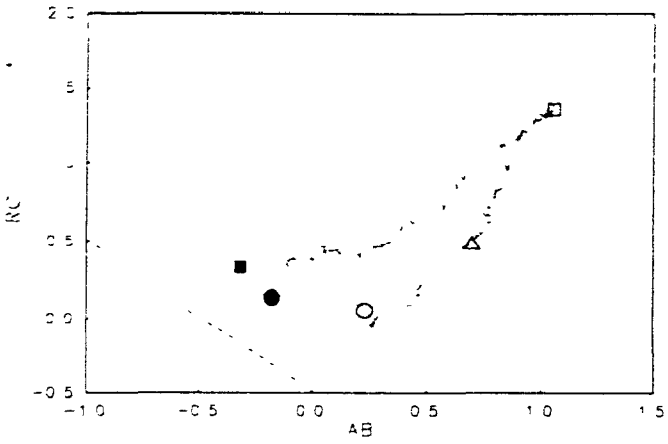


Figure 9.12 c Konno-Mead diagram for A4. RC displacement is plotted v AB displacement. All units are arbitrary.

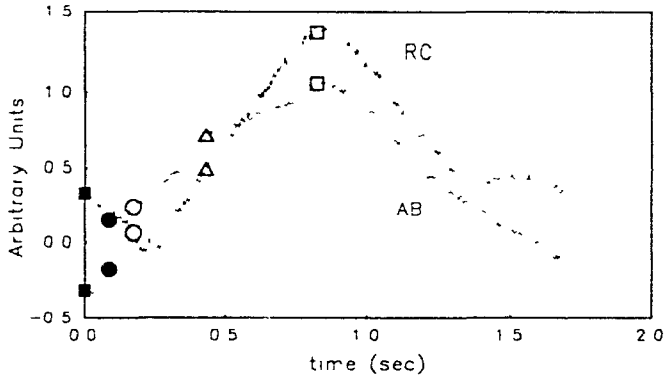


Figure 9.12 d RC and AB displacement are plotted versus time for A4.

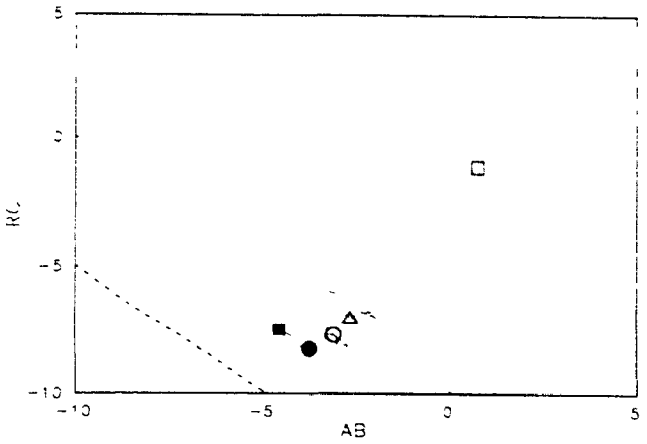


Figure 9.13 c Konno-Mead diagram for N4. RC displacement is plotted v AB displacement. All units are arbitrary.

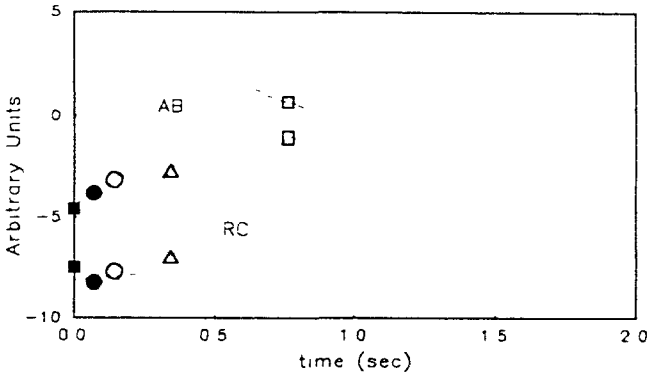


Figure 9.13 d RC and AB displacement are plotted versus time for N4.

only a small portion of the maximal Pes swing has been achieved and the Pga swing is in the positive direction The athlete, from 10% to 25% of Ttot, demonstrates a relatively unchanged negative Pes swing, whereby Pga is moving in the positive direction Inspiratory flow is maintained at a constant peak value In contrast, the normal subject is still experiencing a negative Pes swing, and ΔPga and peak inspiratory flow are relatively stable From 25% Ttot to the end of inspiration, the athlete demonstrates both positive ΔPes and ΔPga In the normal subject, Pes reaches its maximum negative value at the end of inspiration, and the ΔPga has reversed to a negative direction

Analysis of the corresponding Konno-Mead diagram **[fig 9 12 c]** and separate RC and AB displacements v time **[fig 9 12 d]** for A4, demonstrates large AB displacement outwards from 0 to 10% of Ttot, with concurrent RC paradoxical movement inwards N4 demonstrates a similar AB breathing pattern, also with RC paradoxical movement inwards **[fig 9 13.c]** and **[fig 9.13 d]** From 10% Ttot to the end of inspiration, both subjects demonstrate continuing AB displacement outwards now accompanied with similar outward RC movement At end inspiration, both RC and AB are at maximal outward displacement

9.14.2 Mechanics of Breathing in COPD Patients

Within the patient group studied, 5 patients (P1,P2,P4,P5,P7) were defined as low dyspnea responders, based upon their dyspnea response to ΔPes/Pcap, whereas the remaining two patients (P3,P6) were defined as high dyspnea responders **(see 9 7 2)**

9.14.2.1 Low Responding Patients versus High Responding Patients

Macklem diagrams (Pes v Pga) are presented for a representative breath of a low responding patient (P2) **[fig 9 14 a]** and a high responding patient (P3) **[fig 9 15 a]** The corresponding inspiratory flows, Pes and Pga swings are also individually plotted as a function of time for P2 **[fig 9 14 b]** and P3 **[fig 9 15 b]** The Konno-Mead diagrams (RC v AB) for the same breath of P2 and P3 are presented in **fig 9 14 c** and **fig 9 15 c** respectively The corresponding RC and AB displacements as a function of time are individually plotted for P2 **[fig 9 14 d]** and P3 **[fig 9.15 d]** respectively

Comparing the Macklem diagrams of the low responding patient (P2) **[fig 9 14.a]**

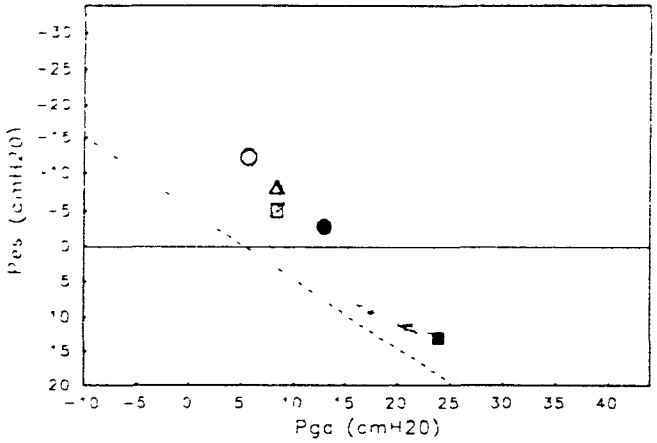


Figure 9 14 a Mackiem diagram for low responding patient (P2) Pes is plotted versus Pga

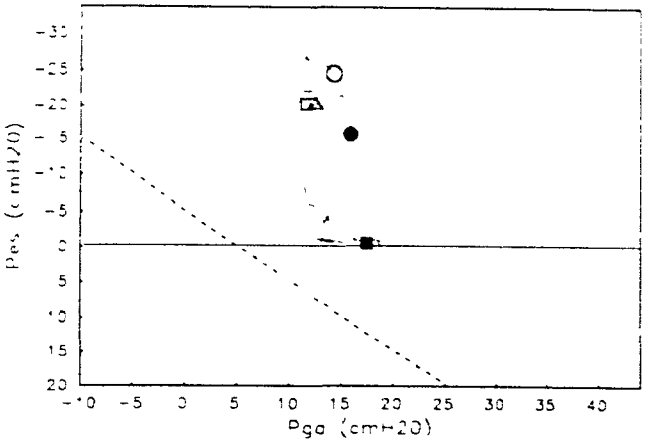


Figure 9 15 a Mackiem diagram for a high responding patient (P3) Pes is plotted versus Pga

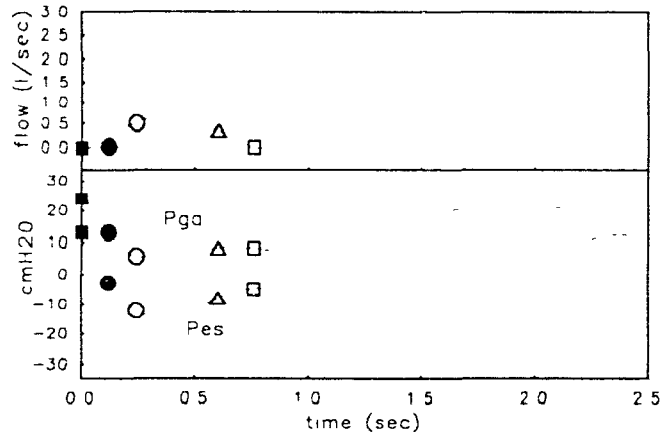


Figure 9 14 b Inspiratory flow, Pes and Pga are individually plotted versus time for P2

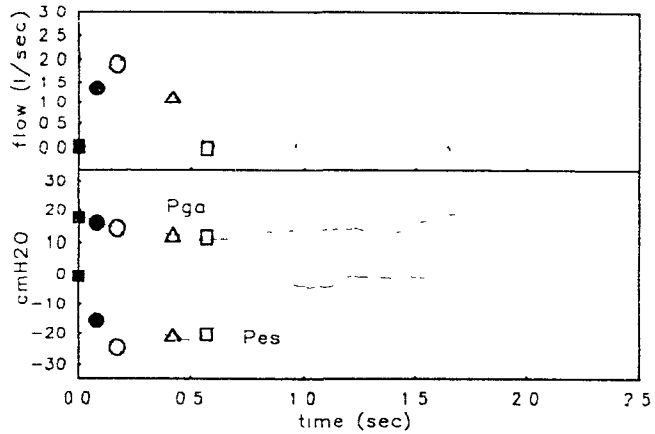


Figure 9 15 b Inspiratory flow, Pes and Pga are individually plotted versus time for P3

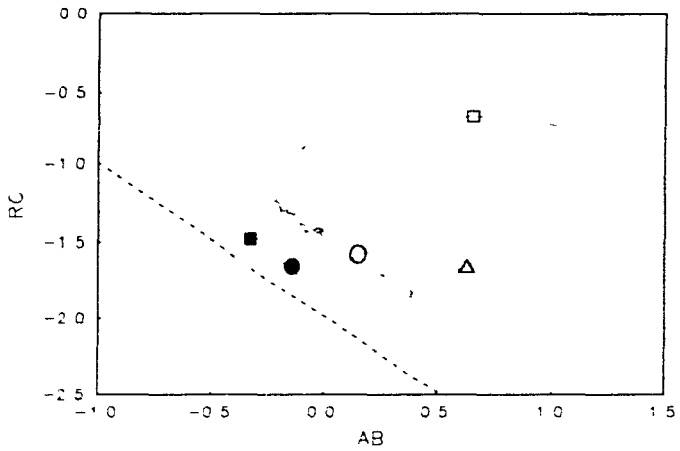


Figure 9 14 c Konno–Mead diagram for P2 RC displacement is plotted v AB displacement All units are arbitrary

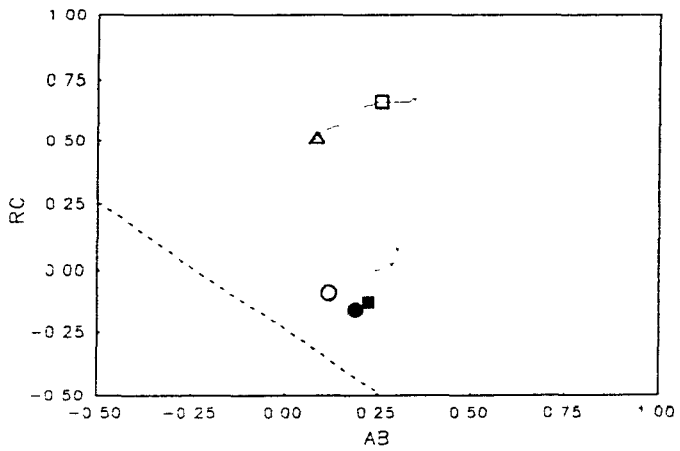


Figure 9 15 c Konno–Mead diagram for P3 RC displacement is plotted v AB displacement All units are arbitrary

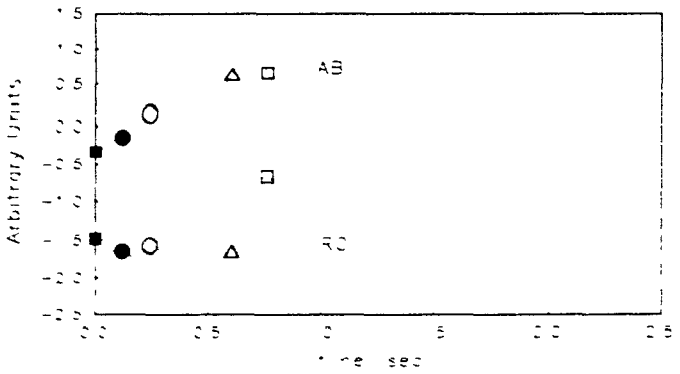


Figure 9 14 d RC and AB displacement are plotted versus time for P2

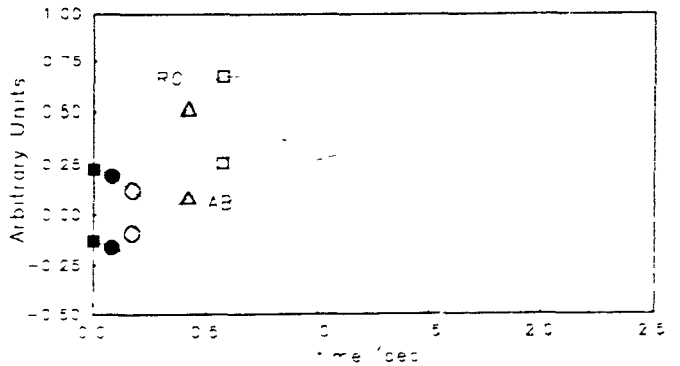


Figure 9 15 d RC and AB displacement are plotted versus time for P3

and high responding patient (P3) **[fig 9 15.a]**, it is observed that P2 begins inspiration from a very large positive end expiratory pleural pressure (EEP) whereas P3 begins inspiration from 0 cmH20 Pes Within 5% of the Ttot, P2 has achieved a very large negative Pes swing, with a parallel large negative Pga swing, with the corresponding Pes v Pga plot lying very close to an iso Pdi=0 line Pes has reached 0 cmH20, whereby inspiratory flow begins **[fig 9 14 b]** In contrast, P3 experiences a large negative Δ Pes, with relatively no change in ΔPga with the first 5% of Ttot **[fig 9 15 b]** Within 10% of Ttot, P2 has achieved peak negative Pes, peak negative Pga and reached the peak of flow acceleration Similarly, P3 has achieved peak negative Pes and peak inspiratory flow, however, ΔPga is still relatively unchanged (ΔPga=0) From 10% to 25% of the Ttot, P2 demonstrates a positive ΔPes with a very slight positive ΔPga P3 also demonstrates a positive ΔPes, however a very small negative ΔPga Inspiratory flow is decreasing for both subjects From 25% Ttot to end inspiration, P2 demonstrates a relatively unchanging ΔPga and slightly positive ΔPes, whereby P3 demonstrates parallel unchanging ΔPes and ΔPga

Analysis of the corresponding Konno-Mead diagram **[fig 9 14 c]** and separate RC and AB displacements v time plot **[fig 9 14 d]** for P2, demonstrates a predominantly AB pattern of breathing In contrast, P3, **[fig 9.15 c]**, **[fig 9 15.d]**, presents with a predominantly RC pattern of breathing Comparing the timing of RC and AB displacements, within the first 5% of Ttot, P2 demonstrates a large outward AB movement with simultaneous inward RC paradoxical movement P3 demonstrates very little RC or AB displacement From 5% to 25% of Ttot, continuing large AB outward movement is observed for P2 with very little concurrent RC displacement P3 presents with exactly the opposite pattern RC displacement is largely outward whereas AB is moving inwards in a paradoxical fashion From 25% Ttot to end inspiration, P2 demonstrates outward RC displacement, reaching peak maximal outward displacement at end inspiration In contrast, only from 25% Ttot to end inspiration does P3 demonstrate outward AB movement coinciding with the continuing RC expansion

CHAPTER 10 DISCUSSION

10.1 Limitations of Study Design

A major limitation of this study's design is the limited number of subjects being evaluated While a total of fifteen subjects is appropriate in overall analysis, the division of this sample population into three distinct smaller groups poses a problem in making any statistical conclusions concerning the population general

The purpose of this study, however, was not to take the underlying statistical results and make specific inferences and statistical conclusions about the general population What this study did attempt to do was to address differences both between and within the athletic, normal and patient groups studied and to identify possible parameters (both quantitative and qualitative) which could explain observed differences This study also dealt with the qualitative analysis of respiratory muscle coordination and attempted to add a qualitative interpretation to the results observed for each subject studied

A large variability in measured values is to be expected when one is performing psychophysical scaling tests Although all subjects' data was included in group mean values, it was often observed that one subject (for example N3 of the normal group), consistently presented data which was different from the remaining subjects within his group Although no statistical significance can be ascertained given the small sample sizes, these differences were pointed out in the respective results sections (ie section 9 2 2) to demonstrate that, in the case of N3, he appeared to present data which was more similar to the athletes than to the normal subjects This point is important given the purpose of this study

10.2 The Perception of Dyspnea during Exercise

In any study requiring a subject to perceive and scale their levels of breathlessness during exercise, there is always the possibility that leg fatigue, pain or other motivational factors may influence the subject's estimation of the investigated sensation Indeed, motivation and psychological factors have been demonstrated to affect an individual's perception to various stimuli [229] These factors are very difficult to control for, therefore

it is plausible that they may have played a role in individuals' dyspnea responses during exercise In an attempt to minimize these factors, subjects were given very specific instructions to exclude any other sensations which might arise during the exercise test and to specifically attempt to scale "how short of breath" they were They were also encouraged throughout the exercise test

At maximum exercise, each groups' mean dyspnea ratings were similar to those previously reported [233,247], however, no subject reached a rated dyspnea level of 10, maximal on the Borg scale This fact is not surprising in the normal group, given that leg fatigue would most likely impose a significant limiting factor to the achievement of high levels of exercise on the cycle ergometer Hence, the achievement of high dyspnea levels could have been significantly limited by the normal subjects' inabilities to reach high levels of work Athletes did demonstrate significantly longer endurance times when compared to the normal subjects and achieved significantly higher levels of workload (in watts) [section 9 2.1], yet they reached similar maximum mean dyspnea values COPD patients would be expected to also achieve high levels of dyspnea perception despite lower levels of work and V_E given the increases in work of breathing due to their diseased state Interestingly though, all groups presented with similar mean dyspnea levels at maximum exercise and maximum dyspnea scores of 10 were not observed

There are several explanations why maximum dyspnea scores were not achieved. A rating of 10 (maximal dyspnea) was described to the subjects as representing the worst possible shortness of breath they have ever experienced, therefore it is possible that this explanation in itself biased subjects not to perceive a score of 10 Also, it has been demonstrated that in general, subjects tend to utilize the Borg scale over a narrower range when compared with open scaling methods, possibly due to the effect of the verbal descriptors in the Borg scale imposing a certain threshold of sensation intensity at each level which must be exceeded before proceeding to the next digit Furthermore, the Borg scale demonstrates an inherent ratio bias which tends to restrict scores to the lower half of the scale [232] A 5 on the Borg scale is verbally linked as "severe"

Subjects were asked to rate their dyspnea levels each minute, which may have been too long an interval Each subject's maximum dyspnea score was recorded for only the final

complete minute of exercise The final partial minute of exercise might have produced rapid increases in dyspnea perception, but the recording interval would have been insensitive to this.

Previous investigators have proposed that COPD patients demonstrate blunted sensitivity when estimating added loads to breathing [182] while others contend that normal perceptual mechanisms exist [210] If COPD patients do in fact experience blunted sensitivity to added loads, an analogy could be drawn to their ability to perceive dyspnea This blunted sensitivity most probably would be a direct effect of the loading history of the respiratory system of individual subjects

In the present study, three distinct subject groups were studied, all presenting with three very distinct respiratory loading histories Elite athletes undergo daily endurance training to their maximum Therefore they experience a type of "chronic" loading of their respiratory system, yet present with normal pulmonary and respiratory muscle function to overcome these loads imposed by physical activity Normal sedentary subjects do not experience daily imposed loading of their inspiratory muscles when compared to athletes, yet they too present with normal lung and respiratory muscle function In contrast, COPD patients experience chronic loading of their respiratory system, dependent on the degree of obstruction, and demonstrate limitations in both pulmonary and respiratory muscle function.

10.2.1 Dyspnea versus Work

Based upon the results of this study, patients did perceive significantly higher dyspnea levels than either the normals or athletes for a given level of absolute work measured in watts However, when individual subjects' achieved workloads were normalized as a percentage of the maximum workload that subject attained, no difference existed between any group in dyspnea levels measured [see section 9 2 2] Differences, though, did exist in dyspnea responses to increasing normalized work COPD patients demonstrated lower, or blunted perceptual sensitivity to dyspnea with increasing normalized work. Inferring from this observation, though, that COPD patients have blunted perceptual sensitivity is premature

No evidence by previous investigators has demonstrated that dyspnea is a direct consequence of workload Rather, studies have focused on the dyspnea relationship to the ventilatory levels achieved during an exercise test

10.2.2 Dyspnea versus Ventilation

As previously demonstrated by other investigators **[165,240,249,250,251, 252,253,254]** these results also display a strong correlation between dyspnea perception and ventilation, and confirm that for a given level of V_E, COPD patients experience higher intensities of breathlessness However, a large inter-subject variation with considerable overlap between individuals of each of the three groups existed when the dyspnea responses to ventilation (V_E/FVC and V_E/MVV) were examined Patients presented with significantly higher mean V_E/FVC and V_E/MVV at all levels of absolute work, yet when workload was normalized as a percentage of maximum, no differences existed between observed V_E/FVC or V_E/MVV for a given level of normalized work Where differences were observed was in the rate of change of the ventilatory response of the groups Patients presented with significantly lower mean rates of increase in both V_E/FVC and V_E/MVV to increasing workload, normalized as a percentage of maximum This observation is not surprising given that COPD severely limits ventilatory increases during exercise

What was surprising was that when dyspnea was examined, no differences in the dyspnea response to changes in either V_E/FVC or V_E/MVV were observed between the athletic, normal or patient groups, appearing to contradict the proposals that COPD patients demonstrate blunted perceptual sensitivity Similar to previously reported studies, though, a lot of within group variability did exist in observed dyspnea responses Indeed, some individual patients actually presented with higher dyspnea responses to changes in V_E/FVC than either athletes or normals

Although COPD patients demonstrated similar dyspnea responses to ventilation, the loads placed upon the inspiratory muscles to achieve a given level of ventilation are significantly increased The mechanical work of breathing is increased whereby larger pleural pressure changes are necessary to overcome the increases in both the frictional and elastic work of breathing

10.2.3 Dyspnea versus Pleural Pressure

To further investigate the idea of perceptual blunting, the relationship of dyspnea to changes in $\Delta Pes/Pcap$ was addressed if dyspnea is directly related to the outgoing motor command to the inspiratory muscles as previously hypothesized, then the concept of perceptual blunting should not be applied to studies evaluating the relationship of dyspnea versus ventilation but rather, the changes in dyspnea which occur with the increasing pressure changes required to bring about that level of ventilation

As a group, the patients did not demonstrate differences in dyspnea sensitivity to $\Delta Pes/Pcap$ when compared to the athletic group but they did demonstrate lower sensitivity when compared to the two normal subjects defined as high dyspnea responders As discussed in the results section 9 7.2 3, though, a lot of variation in dyspnea response did exist within the patient group This variation is not surprising, given the expected variability recognized when evaluating any perceptual sensitivity What was interesting was that within the patient group, some patients presented with extremely low dyspnea responses to changes in pressure (P1,P2,P4,P5,P7) and did appear to demonstrate a blunted dyspnea response to increases in $\Delta Pes/Pcap$ when compared to all other subjects Two patients, though, did not demonstrate this apparent perceptual blunting, but instead demonstrated similar dyspnea responses as the athletes and low dyspnea responding normals In conclusion, while it appears that some COPD patients do appear to demonstrate perceptual blunting of dyspnea, others respond as normal subjects Therefore, this study does not confirm that COPD patients as a group demonstrate blunted perceptual sensitivities to dyspnea

One limiting factor of this study lies in the age disparity between each group A decline in the perceptual sensitivity of added elastic and resistive loads has been demonstrated with increasing age **[208,209,210]**, however, it is unknown if a similar age-related blunted sensitivity exists for dyspnea perception All of the COPD patients studied were signif ntly older than both the athletes and normals Despite this, though, some patients demonstrated very similar dyspnea perceptions when compared to some normal and athletic subjects Others, though, did appear to demonstrate perceptual blunting (when dyspnea was related to $\Delta Pes/Pcap$ as discussed above) Although age disparity could be

a possible explanation for the lower dyspnea responses observed in the apparent perceptually blunted patients, it fails to explain the normal or even enhanced dyspnea responses observed in other COPD patients

The normal subjects were older than the athletes, yet two normals were defined as high responding subjects Similarly, the high dyspnea responding patients were significantly older than the athletes and normals, yet displayed dyspnea responses similar to both the athletes and low responding normal subjects

In conclusion, some COPD patients' sensitivities to increasing dyspnea appears blunted when dyspnea is examined as a function of pressure changes; however, the observed differences in response when all subjects (athletes, normals and patients) are considered cannot be explained solely by age disparities

10 3 Factors Limiting Exercise

10.3.1 Ventilation

As previously discussed in the literature review, the ventilatory system is not usually regarded as a limiting factor of exercise in normal subjects, however in patients with COPD, their severely limited ventilatory capacity will result in a reduced exercise capacity **[89,91,93,100,294]** Patients demonstrated similar mean VE at quiet breathing when compared to athletes and normals, similar to results of previous investigators **[90]** Throughout the progression of the exercise test, however, further increases in VE were significantly limited

Normalizing VE as a percentage of the FVC takes into account the differences in both lung size and ventilatory limitations imposed on the patients by their disease Patients' VE/FVC at rest was significantly higher than both athletes and norma' However, at maximum exercise VE/FVC was similar to the normals yet lower than that of the athletes. Examining VE/FVC as a function of the % of maximum achieved work, it was demonstrated that although presenting with similar VE/FVC for a given % work throughout most of the exercise test, the rate of increase of VE/FVC was still significantly reduced

Using the estimated maximum voluntary ventilation (MVV) to indicate the maximum

ventilatory capacity of the respiratory system, patients presented with significantly lower MVV when compared to both athletes and normals One limitation of this estimated MVV was that it was derived mathematically by utilizing the equation, FEV_1*42 The FEV_1 is not limited by reduced respiratory muscle strength whereas a true measured MVV may be Therefore, the lower MVV's observed in the patients may have been a direct consequence of solely their obstruction and not necessarily due to reduced respiratory muscle strength The measured VE of patients at rest accounted for a mean value of 32 2% of their ventilatory capacity, increasing to a high of 81 ± 33% at maximum exercise Thus, patients were utilizing a much higher % of their ventilatory capacity and often exceeded their maximum sustainable ventilation In contrast, both athletes and normal subjects, were working at, but not exceeding their maximal sustainable ventilation of approximately 60% of their predicted MVV at maximum exercise

10.3.2 The Inspiratory Muscles

The role of the inspiratory muscles as potential factor limiting factors of exercise endurance must also be considered The studied patients presented with moderate to severe airway obstruction, based upon the observed reductions in their measured FEV_1/FVC, and were extremely hyperinflated at rest, indicated by the disproportionate increase in the measured RV/TLC As previously discussed, hyperinflation compromises the ability of both the inspiratory intercostals and the diaphragm to generate the necessary force for tension development

Utilizing the measured maximum inspiratory pressure (MIP) at FRC as an index, the patients demonstrated significant reductions in inspiratory muscle strength compared to both athletes and normals Also, the patients' abilities to generate maximum transdiaphragmatic pressures were significantly limited, indicative of their hyperinflated state and subsequent diaphragmatic inefficiencies

In conclusion, these results indicate that although differences in lung volumes (ie patients demonstrate reduced VC due to large increases in RV as well as variations due to body size) and the airway obstruction characteristic in COPD do account for some of the

observed limitations to increasing $\dot{V}E$ in the COPD patients, other contributing factors must be considered Ventilatory limitations, significant reductions in inspiratory muscle strength, reduced ventilatory reserve coupled with dyspnea probably act together to play a major role in the observed exercise limitations of COPD patients

When considering exercise limitation of normal and athletic subjects, on average they had just achieved their maximum sustainable ventilation at the same time as maximum exercise was reached, thus it appears that ventilation alone was not a limiting factor for these subjects Indeed, peripheral limb fatigue and dyspnea may have played significant roles in the limitation of exercise

One major limitation to the above interpretation of possible limiting factors of exercise lies in the methodology of this study Cardiovascular data did not play a role in the analysis given that the main issue being addressed was the role of respiratory muscle coordination to dyspnea Therefore parameters such as VO2, VCO2, SaO2, the anaerobic threshold and exercise induced hypoxemia were not measured and inferences concerning their role in limiting exercise cannot be commented upon.

10.4 Mechanisms of Dyspnea

10 4.1 The Relationship of Dyspnea to Pressure Changes

When evaluating possible mechanisms which underlie dyspnea perception, it can be noted that a relationship between dyspnea and ventilation does exist for individual subjects It is concluded, though, that dyspnea is not a direct function of the actual ventilation or percentage of capacity being utilized per se Since ventilation is the final output of the respiratory system, it is reasonable to believe that dyspnea perception will be more closely linked to some mechanism involved in achieving that given ventilation Therefore, the relationship of dyspnea to changes in both pleural and gastric pressures is examined in more detail

Previous investigators [219,233,248,264], have demonstrated a positive linear relationship between dyspnea and pleural pressure (Pes), normalized by the MIP in both normal and COPD subjects However, utilizing MIP as the normalization factor presents

serious limitations. MIP is a measure of the static, maximum pressure the inspiratory muscles are capable of generating, usually measured at FRC

Pleural pressures measured during this study and those previously mentioned, however, were under the dynamic conditions of exercise It has long been recognized that the ability to generate pleural pressure decreases both with increasing inspiratory flow rates **[267,269]** and increasing lung volumes [266] Thus, normalizing ΔPes measured during an exercise test by MIP would theoretically underestimate the proportion of maximum pleural pressure being expended to achieve a given ventilation

Normalization of ΔPes by the maximum capacity the inspiratory muscles are capable of generating at a given inspiratory flow and volume (P_{cap}) is an attempt to correct for this limitation Our results demonstrate a strong, linear correlation between dyspnea and ΔPes/MIP and between dyspnea and $\Delta Pes/P_{cap}$ Both methods of normalization result in similar observed differences in the dyspnea responses both within groups and between groups Athletes presented as low dyspnea responders, two normals presented as low and two as high dyspnea responders, while within the patients group, five patients presented with a low and two with a high dyspnea response Comparison of the two methods of normalization, however, demonstrated that MIP normalization did underestimate individual subjects' dyspnea responses to ΔPes This underestimation was significant in the athletic and normal groups but not in the patient group This is not surprising given the fact that athletes and normals are able to achieve large increases in both their inspiratory flow rates and volumes to meet the demands of exercise, whereas the patients are severely limited in their ventilatory response It should be pointed out, though, that the full negative effects of increases in inspiratory volumes which occurs during exercise in both normal and athletic subjects will be somewhat offset by their ability to reduce EELV below FRC This would somewhat decrease the volume effects upon P_{cap}, but only up to a volume of approximately 10% TLC

In conclusion, P_{cap} is a more accurate normalization tool for both normal and athletic subjects when assessing pleural pressure changes during progressive exercise testing

10 4 2 Dyspnea and the Mechanics of Breathing

The simultaneous measurements of esophageal pressure (as an estimate of pleural pressure) and gastric pressure (as an estimate of abdominal pressure) coupled with rib cage and abdominal wall displacements provides a qualitative means of inferring both respiratory muscle mechanics and coordination Limitations of this method of analysis lies in its inability to identify the quantitative contribution of the diaphragm and the "intrinsic" muscle groups when antagonistic muscle activity is present such as seen during exercise **[98,147]**

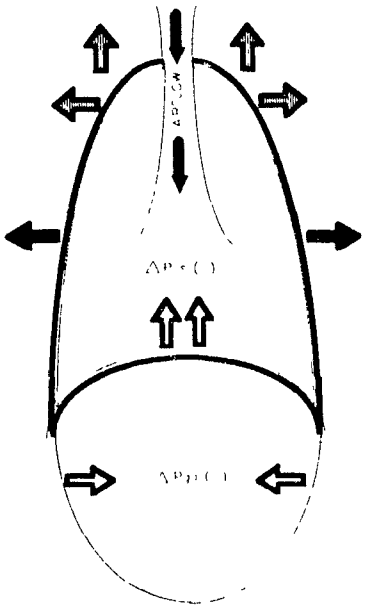
In the results section, representative breaths are presented for numerous subjects at iso-dyspnea levels of 5 Comparable results are obtained at other points during the exercise for each subject, however, for simplicity, only single breath representations are presented The relative workload at which a subject experiences a dyspnea level of 5 is not relevant to the following discussion concerning mechanics of breathing

All subjects demonstrated some degree of a negative gastric pressure swings upon early inspiration, except for A3 and N4 who presented with a pattern of predominantly $\Delta Pga = 0$ during early inspiration, as exercise intensity increased Patterns of negative gastric pressure generations have been reported in both normal subjects during exercise, during hyperventilation induced through re-breathing **[145,295,296]**, and in asthmatic **[57]** and COPD patients both during exercise and at quiet breathing **[98,297]** There are several possible breathing strategies which would account for negative ΔPga swings during early inspiration **[fig 10.1 a, fig 10 1 b, fib 10.1 c]**

The first would be an inspiratory effort initiated by active intercostal/accessory muscle contraction, where the negative pressure generated in the thorax is transmitted to the abdominal space through a passive diaphragm **[fig 10.1 a]** Examining the relative motion of both the RC and AB, RC expansion would be observed with a coinciding paradoxical inward movement of the AB, assuming the abdominal muscles are relaxed.

The second breathing strategy could be the passive relaxation of the triangularis sterni muscle upon early inspiration, again resulting in negative ΔPpl being transmitted through a passive diaphragm, resulting in a negative ΔPga swing **[fig 10 1 b]** A similar RC out, paradoxical AB inward motion would be observed, again assuming abdominal muscles

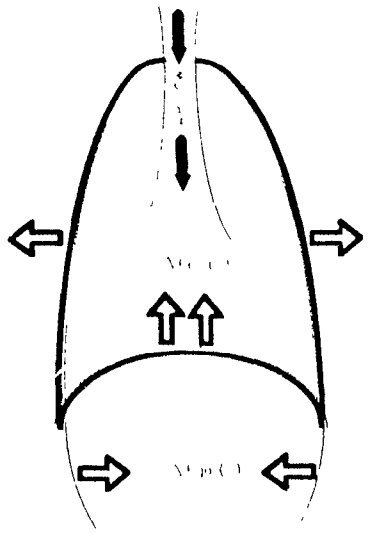
INSPIRATORY MECHANICS USING
INTERCOSTAL & OR ACCESSORY SCALENE MUSCLES



ACTIVE ACCESSORY/SCALENE MOVEMENT
ACTIVE INSPIRATORY INTERCOSTAL MOVEMENT
PASSIVE MOVEMENT

Figure 10.1a

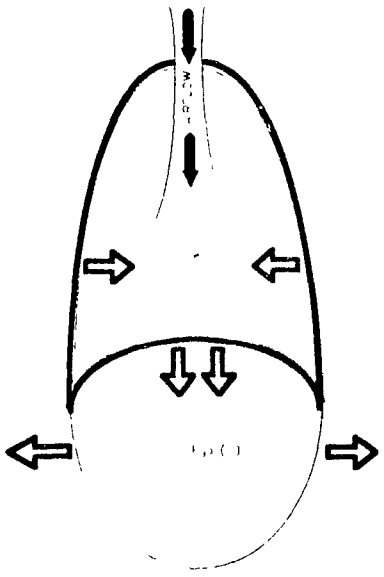
INSPIRATORY MECHANICS DURING
PASSIVE RELAXATION OF DIAPHRAGM & STERNI



PASSIVE MOVEMENT

Figure 10.1b

INSPIRATORY MECHANICS DURING
PASSIVE ABDOMINAL MUSCLE RELAXATION



PASSIVE MOVEMENT

Figure 10.1c

INSPIRATORY MECHANICS DURING
PASSIVE ABDOMINAL MUSCLE RELAXATION
COUPLED WITH DIAPHRAGMATIC CONTRACTION

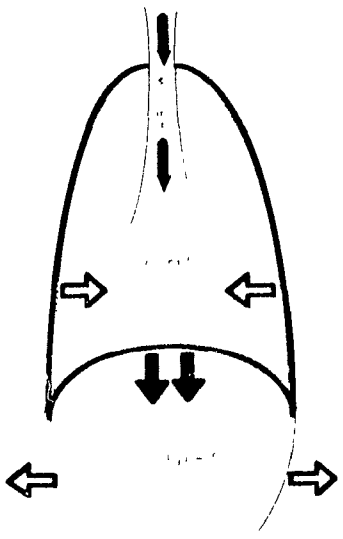


Figure 10.1d

are relaxed To the best of my knowledge this hypothetical breathing pattern has never been demonstrated in normal subjects

The third strategy involves the employment of the abdominal muscles in an inspiratory "accessory" role Following abdominal muscle contraction during expiration, their subsequent relaxation upon early inspiration would result in a negative ΔPga swing **[fig 10 1 c]** Thus, during expiration, abdominal muscle contraction acts to store both elastic energy and gravitational energy in the diaphragm/abdominal wall and through the subsequent relaxation upon inspiration, the gravitational potential energy of the abdominal contents being pulled caudally is sufficient to accelerate diaphragmatic descent and to decrease intrathoracic pressure If the rib cage muscles are relaxed, an inward paradoxical movement would be observed, whereas if the rib cage volume increases or remains relatively constant, this would indicate the switching of intercostal activity from expiratory to inspiratory **[98]**

It has been proposed that a 0 cmH20 change in ΔPga during early inspiration is a result of the coordination of release of abdominal muscle tone coupled with simultaneous diaphragmatic contraction against minimal abdominal impedance **[298]** If this were the case, outward AB movement would be observed upon early inspiration **[fig 10.1.d]**, and consequent RC movement would be dependant on the level of activity of the inspiratory intercostal/accessory muscles

The importance of the abdominal muscles as "accessory" muscles to inspiration is now recognized Increased expiratory abdominal muscle recruitment during exercise has been well documented in both normal and COPD subjects Increased abdominal muscle recruitment causes a decrease in end-expiratory lung volume below the normal FRC in normal subjects by approximately 10% of TLC both during exercise to maximum and during inspiratory loading **[39,79,299,300,301,302]** In contrast, it has been demonstrated that expiratory muscle recruitment during exercise in COPD patients is largely ineffective in reducing EELV, due to expiratory flow limitations imposed by the obstruction **[89,97,98,122]**, and dynamic hyperinflation results in increases in end expiratory pressure

It is argued, therefore, that in order for the abdominal muscles to adopt an "inspiratory" role, increasing positive end expiratory pressures in normal subjects is an

unavoidable occurrence. In normal subjects, the reduction of resting lung volume below FRC permits the elastic outward chest wall recoil to aid the proceeding inspiration In contrast, though, the acute hyperinflation which occurs during exercise in the majority of COPD patients acts to place the inspiratory muscles at an even more shortened, disadvantageous initial length position for the proceeding inspiration

Most investigators have stressed the role of expiratory abdominal muscle recruitment on optimizing resting diaphragmatic length and improving its inspiratory efficiency to expand the rib cage through an increase in the zone of apposition **[7,32,57,145,295,296,303]** However, few investigators have emphasized the role of inspiratory passive abdominal muscle relaxation in actually contributing to the inspiratory pressure generation **[98]** Such a function would prove to be of great significance, especially in COPD patients, given that reduced inspiratory muscle strength coupled with the mechanical inefficiency of requiring larger pleural pressure swings to achieve a given ventilation, act to place their inspiratory muscles at risk to develop fatigue

The significant role of respiratory muscle function in the perception of dyspnea has been proposed, with previous investigators hypothesizing that dyspnea is the perception of the outgoing motor command to the inspiratory intercostals/accessory muscles **[222,245,259,271,284,285]** Any mechanical readjustment of the breathing pattern which acts to "load" or increase the central motor output towards both the inspiratory intercostals/accessory muscles has been shown to result in higher levels of dyspnea **[271,273,274]**

Theoretically, therefore, any readjustment of respiratory muscle activity which would serve to decrease the load placed upon the inspiratory intercostal/accessory muscles would therefore reduce the amount of central motor output directed towards these muscles and would theoretically result in a lower dyspnea perception Passive abdominal relaxation upon early inspiration would serve such a purpose

Indeed from our results, it appears that during progressive exercise, the utilization of abdominal muscle relaxation during early inspiration does play a significant role in reducing the dyspnea response of subjects to changes in pleural pressure This conclusion is based upon numerous qualitative and quantitative observations made throughout the

subjects' individual progressive exercise tests

It appears that the athletes, low dyspnea responding normal subjects and low dyspnea responding patients all utilized some degree of passive abdominal muscle relaxation during early inspiration, whereas high responding normals and high responding patients did not employ this method to make a significant contribution to the necessary pleural pressure generation

All subjects studied presented with positive increases in both end expiratory pleural pressures (EEP) and gastric pressures, combined with inward RC and AB displacement, indicative of a combination of increased expiratory intercostal muscle recruitment and abdominal muscle recruitment and in the case of the COPD patients, dynamic hyperinflation

All athletes, low dyspnea responding (LDR) normal subjects and LDR patients demonstrated AB displacement outward upon early inspiration as observed in the presented Konno-Mead diagrams In addition, inward paradoxical or virtually no RC movement was observed in these abdominal breathers during the early phase of inspiration until inspiratory flow and volumes were increased This time readjustment of the abdomen leading the rib cage and with the rib cage paradoxically moving inward upon early inspiration has been observed in normal [302] and COPD patients [98,297,304,305] during progressive exercise and loading experiments Examining the pressure generation profile, presented in Macklem diagrams, a large negative ΔPga swing and concurrent negative ΔPes swing is demonstrated The observed combination of RC and AB displacement, coupled with the observed pattern of pressure generation implies that passive abdominal muscle relaxation is occurring, providing the mechanism for pressure changes The similarity in both pressure generation profiles and RC and AB motion when athletes are compared with LDR COPD patients is striking In the athletes and LDR patients, for example, these negative pressure swings occurred within the first 10% of the time of the breath, and upon examining the Macklem diagram, the pressure generated during this early phase lies very close to an iso Pdi = 0 line It is therefore possible to infer that very little change in transdiaphragmatic pressure is occurring in this early phase of inspiration and that minimal diaphragmatic activation is required In contrast, the high dyspnea responding (HDR) normals and HDR

COPD patients, despite achieving negative pleural pressure swings, demonstrated minimal gastric pressure swings during early inspiration Examining the relative motion of the RC and AB, outward RC movement is observed upon early inspiration with no outward movement or inward paradoxical movement of the AB Therefore, it can be inferred that in these high dyspnea responding subjects, the RC muscles are actively contracting to generate the necessary change in pleural pressure

Following these generalized observations, it is possible to divide early inspiratory pressure generation into two phases The first is the "pre-inspiratory flow" phase of pressure generation and indicates the mechanisms utilized to return the respiratory system to a level whereby inspiratory flow can be initiated Resistive and elastic loading studies have demonstrated that the perception of just detectable loads occurs very early in the inspiration, close to peak flow [179,180] Applying this concept to the present study, the phase of pressure generation from 0 to peak flow acceleration is also explored

All subjects presented with some degree of increases in pleural end expiratory pressures (EEP) as exercise progressed These observed increases were due to either increased expiratory muscle recruitment and a reduction in end expiratory lung volumes below FRC, as occurred in the normal and athletic subjects, or due to the combination of increased expiratory muscle activity coupled with dynamic hyperinflation, previously observed to occur in COPD patients during exercise

Examining the pre-inspiratory flow phase of pressure generation, it was observed that all athletes and N3 (LDR) presented with lower dyspnea responses to the positive end expiratory pleural pressures (EEP) when compared to high responding normals N1, N2 and the LDR subject N4 Similarly, the LDR patients (P1,P2,P4,P5,P7) presented with low dyspnea responses to EEP when compared to the HDR patients (P3,P6) Of the HDR patients, P3 actually presented with an inconsistent relationship of dyspnea to EEP while P6 presented with a response similar to N1,N2 and N4

Evaluating actual EEP measured, some athletes presented with much higher EEP when compared to the normal subjects, four of the seven patients who presented with the highest EEP were also LDR Mechanically, increasing EEP causes work to be performed on the lung which would produce no ventilation and the subsequent high levels of

intrathoracic pressure may impose a limitation to cardiovascular function **[91]** It is therefore surprising that in general, the low dyspnea responders were the subjects who were faced with the largest mechanical impedance to overcome in order for inspiratory flow to begin As previously mentioned, both athletes and normal subjects have the benefit of increased outward chest wall recoil to aid in overcoming the EEP, but the COPD patients cannot rely on such a mechanism Passive abdominal relaxation in COPD patients may thus constitute an optimal response of the respiratory system aimed at achieving the maximum ventilation possible in the face of a severe mechanical impediment **[98]** Conversely, in the athletes, abdominal muscle relaxation would be additive to the outward chest wall recoil which occurs when lung volumes are below FRC The two coupled together would result in inspiratory mechanics which are very energy efficient

Three of the four athletes (A1,A2,A3) and one low responding normal (N3) presented with much faster negative rates of change in gastric pressure ($\Delta Pga/\Delta t_{PRE}$) when compared to the remaining subjects The one remaining athlete (A4) and low responding normal (N4) both presented with lower rates of gastric pressure change and in the case of the normal, ΔPga was in the positive direction However, the role of abdominal muscle relaxation, in these two subjects was still significant (as seen in the respective Konno-Mead diagrams) Abdominal muscle recruitment during expiration would not only place the diaphragm at a more lengthened position but the diaphragm would be primed for subsequent inspiratory contraction Indeed, it has been shown that the force developed by a muscle when it shortens after being stretched is greater than that developed at the same speed and length when starting from a state of isometric contraction **[306]** Thus as the abdominals relaxed the diaphragm was faced with optimal conditions in which to contract downwards A wide variability existed within the patient group when the $\Delta Pga/\Delta t_{PRE}$ was examined at maximum exercise As seen on Table 9 3, P2 (LDR) presented with a similar rapid rate of change in gastric pressure as seen in the athletic subjects The remaining subjects presented with varying rates of change, however, it should be noted that the two lowest observed rates of change were by the two HDR patients (P3,P6) These two subjects also demonstrated large variations in their breath to breath measured $\Delta Pga/\Delta t_{PRE}$, whereas P4,P4,P7 (all LDR) presented with relatively consistent $\Delta Pga/\Delta t_{PRE}$ as inferred from the

small standard deviations about the means P1 (LDR) demonstrated some very rapid changes in gastric pressures while in other breaths, he demonstrated relatively no change

The rate of change of negative pleural pressure ($\Delta Pes/\Delta t_{PRE}$) in this pre inspiratory flow phase also appeared to be related to the ability to utilize abdominal muscle release In general, the athletes all demonstrated very rapid $\Delta Pes/\Delta t_{PRE}$, as did four of the five low responding patients (P1,P2,P4,P7) It is also seen that those subjects who experienced the larger development of EEP during exercise, also demonstrated faster $\Delta Pes/\Delta t_{PRE}$ It can be speculated that abdominal muscle relaxation provided an accelerative mechanism, permitting a more rapid rate of change of pleural pressure to overcome the EEP and to initiate the next inspiration

Similar to this concept, Dodd *et al* **[98]** hypothesized that at the onset of inspiratory flow at the mouth, the diaphragm/abdomen have already acquired a descending velocity, which must be additive to that produced throughout inspiration by the release of gravitational energy They also proposed that the elastic energy derived from thoracic gas decompression, added to the "sling shot" effect of abdominal muscle relaxation would result in a more rapid development of negative pleural pressure on inspiration than would otherwise be possible These results appear to corroborate this hypothesis

When comparing the maximum rate of change of pleural pressure achieved from the onset of inspiratory flow to peak flow acceleration ($\Delta Pes/\Delta t$) at maximum exercise of each subject, it is observed that three of the four athletes (A1,A3,A4) achieved very high $\Delta Pes/\Delta t$ The remaining athlete while achieving a lower $\Delta Pes/\Delta t$ than the others, was the athlete who only reached 80% of his maximum workload When considering the ratio of $\Delta Pes/\Delta t$ to $\Delta Pes/Pcap$, the athletes were able to achieve a much faster rate of change of pleural pressure for a given % change in $\Delta Pes/Pcap$ This supports the idea that abdominal muscle relaxation may in effect "accelerate" the negative change in pleural pressure required for ventilation In contrast, the normal subjects all presented with much lower $\Delta Pes/\Delta t$, regardless of whether they were low or high responders A possible explanation as to why the two normals deemed "low responders" do not exhibit the same accelerative forces working on ΔPes as do the athletes lies in their level of workload achieved Leg fatigue, motivation or other factors previously discussed may have played a limiting role in both of

these subjects and therefore they demonstrated smaller positive increases in EEP. Therefore, they would have had lower levels of abdominal muscle recruitment, coupled with their lower levels of achieved work, thus the possible accelerative force which abdominal muscle relaxation provides would be limited The patients demonstrated similar ratios of ΔPes/Pcap to ΔPes/Δt when compared to normals and indeed, often achieved higher ΔPes/Δt at maximum exercise

It is important, however, to consider the rates of change of gastric pressure ΔPga/Δt which accompany and perhaps contribute to the rate of change of pleural pressure If abdominal muscle relaxation does play a role in reducing dyspnea perception, it would be expected that for a given increase in dyspnea, a concurrent rapid ΔPga/Δt would occur This relationship is expressed by the ratio of Δdyspnea to ΔPga/Δt

Three athletes (A1,A2,A4) and one low responding normal (N3) both presented with strong relationship correlations between dyspnea and ΔPga/Δt throughout the exercise test Also they demonstrated a much faster rate of change in gastric pressure for a given change in dyspnea when compared to both high responding normal subjects (N1,N2) In contrast, again A3 and N4, both low responders presented either a poor correlation or positive (ie ΔPga/Δt >0) ratio As discussed previously, these two subjects demonstrated patterns of either relatively no change in gastric pressure or positive ΔPga swings Looking at the patients, all low responders also demonstrated similar fast rates of change in gastric pressure for a given change in dyspnea, similar to the athletes The two patients termed high responders exhibited much smaller changes in the rate of gastric pressure change for a given change in dyspnea

Qualitatively, looking at subjects who presented with early inspiratory passive abdominal relaxation, it was consistently observed that upon higher levels of work, the generation of peak negative pleural pressure, coupled with the rapid negative gastric pressure swing resulted in the complete acceleration of inspiratory flow to peak values in both athletes and LDR patients If an analogy can be made to the previously mentioned loading studies **[179,180]**, the perception of dyspnea may occur very early in inspiration If this is true, early inspiratory abdominal muscle relaxation is well suited as a "dyspnea limiting" mechanism

Researchers have demonstrated that dyspnea is not directly related to the level of diaphragmatic fatigue [264,271,272] but rather to the "loading" effects that induced diaphragmatic fatigue would impose on the inspiratory intercostal/accessory muscles In the subjects studied, it does not appear as if any subjects achieved above threshold pressure-time indices of the diaphragm, excluding the presence of diaphragmatic fatigue The exception to this is P4, who exceeded the threshold level of 0 15 TTdi This patient, however, demonstrated a strong abdominal relaxation breathing pattern This mechanism would theoretically permit the diaphragm to generate tension with less amount of work being performed, therefore, permitting a TTdi >0 15 to be achieved without impending fatigue

When measuring the pressure-time index of the inspiratory muscles (TTim), several factors must be considered The TTim is based upon the assumption that all of the pleural pressure changes occurring are due solely to active inspiratory muscle contraction Increased expiratory muscle recruitment during exercise would cause an over exaggeration of the measured pleural pressure swings, therefore, the effects of abdominal muscle relaxation on changes in pleural pressure must be considered when evaluating the TTim of subjects during exercise Indeed, from the results, A1,P1,P2 and P4 all present with TTim exceeding the designated inspiratory muscle fatigue threshold of 0 24 However, all of these subjects demonstrated abdominal muscle relaxation, resulting in a portion of the pleural pressure change to be generated passively However, given the design of this study, it is impossible to discern quantitatively what the contribution to pleural pressure changes is being accomplished through abdominal relaxation and by inspiratory muscle activity

Therefore, it appears that passive abdominal recoil not only acts to unload the diaphragm but also to unload the inspiratory muscles, permitting larger pressure generation with little risk of developing inspiratory muscle fatigue In conclusion, it does not appear as if either diaphragmatic fatigue or inspiratory muscle fatigue played a limiting role in exercise

10.7 CONCLUSIONS

These results indicate that dyspnea perception is directly related to respiratory muscle function The hypothesis that dyspnea is a perception of the outgoing motor command to the inspiratory muscles (intercostals/accessories) is one which would provide an explanation for our results

Exercise imposes demands upon the respiratory system, demands which the inspiratory muscles must meet by increasing their force generation, in order to generate the required ventilation Thus, as exercise intensity increases, the inspiratory muscles are faced with increasing ventilatory loads Both athletes and normals demonstrate normal respiratory muscle strength and function, whereas the COPD patient is faced with severe limitations in both endurance and function However, when examining pressure generation and relative RC and AB motion, it is surprising to see the similarity between LDR patients and athletes

The importance of passive abdominal muscle relaxation upon early inspiration has not been directly investigated in the past This study, though, demonstrates that this mechanism indeed appears to play a very important role mechanically. It appears to not only unload both the diaphragm and the inspiratory intercostal/accessory muscles, preventing fatigue at high workloads, but also to provide a very strong accelerative force for pleural pressure generation Subjects who presented with a coordinated pattern of abdominal muscle relaxation presented with lower dyspnea responses to changes in pleural pressure It also can be hypothesized that in some COPD patients, the lower dyspnea response to changes in pleural pressures is a direct result of their adopted breathing patterns and not due to perceptual blunting of sensation In conclusion, passive abdominal muscle relaxation appears to play a significant role in limiting the perception of dyspnea during progressive exercise

SUGGESTIONS FOR FUTURE RESEARCH

1. Perform an epidemiological study, examining the prevalence of early inspiratory abdominal muscle relaxation during exercise in a population of athletes, normal subjects, chronic obstructive pulmonary diseased patients

2. Study the effects on dyspnea perception of abdominal muscle relaxation during another form of exercise (ie. treadmill exercise)

3. Investigate the mechanics of breathing during expiratory resistive loading in normal subjects and the relationship to perceived dyspnea

4 Investigate the effects that early inspiratory abdominal muscle relaxation has on both the timing of and electromyographic activity of the diaphragm

5 Investigate if inspiratory abdominal muscle relaxation has a similar role in the reduction of dyspnea perception during exercise in a group of patients suffering from restrictive lung disease.

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