THE RESPIRATORY MUSCLES:
VENTILATION DISTRIBUTION AND FATIGUE

by

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To My Son ....

Ὁ βίος βραχύς, ἡ δέ τέχνη μακρή,
ὁ δέ καιρός ὀξύς, ἡ δέ πεῖρα σφαλερή,
ἡ δέ κρίσις χαλεπή.

Ἱπποκράτης

Life is short, the Art long,
opportunity fleeting, experience
treacherous, judgement difficult.

Hippocrates

ABSTRACT

Control of ventilation distribution by selective contraction of different muscle groups was studied in upright and horizontal postures. Distribution of gas inspired at FRC was more to dependent lung regions during preferential contraction of the diaphragm, and to nondependent zones during intercostal and accessory muscle activity. In the lateral posture, voluntary diaphragmatic contractions decreased by 85% the vertical gradient of alveolar expansion and decreased the sequential pattern of lung emptying. Fatigue of inspiratory muscles was studied by measuring endurance time (t_{lim}) while breathing through various inspiratory resistances. The inspiratory mouth pressure which could be generated indefinitely (Pm_{crit}) at FRC was ca. 60% of maximal, equivalent to a power of 6.8 Kgm/min. At FRC + ½ inspiratory capacity, Pm_{crit} decreased to 30% of maximal. The transdiaphragmatic pressure (Pdi) that could be generated indefinitely (Pdi_{crit}) was 40% of maximal Pdi. Hypoxia shortened t_{lim} when $Pdi > Pdi_{crit}$.

RESUME

Le contrôle de la distribution de la ventilation par contraction sélective des différents groupes musculaires fut étudié en position debout et horizontale. La distribution des gaz inspirés à CRF prédomina aux régions déclives pulmonaires pendant la contraction préférentielle du diaphragme, et aux zones non déclives au moment où seuls les muscles intercostaux et accessoires s'activèrent. En position latérale, les contractions diaphragmatiques volontaires amoindrirent de 85% le gradient vertical d'expansion alvéolaire et diminuèrent le cycle séquentiel de la vidange pulmonaire. La fatigue des muscles inspiratoires fut étudiée par la mesure du temps d'endurance (t_{lim}) pendant la respiration sous diverses résistances inspiratoires. La pression inspiratoire à la bouche indéfiniment générée (Pm_{crit}) à CRF fut d'environ 60% de son maximum, l'équivalent d'une puissance de 6.8 Kgm/min. Ajoutant ½ capacité inspiratoire à la CRF, la Pm_{crit} diminua à 30% de son maximum. La pression trans-diaphragmatique (Pdi) pouvant être générée indéfiniment (Pdi_{crit}) fut de 40% de la Pdi_{max} maximale. L'hypoxie a raccourci t_{lim} quand $Pdi > Pdi_{crit}$.

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PROLOGUE

This thesis has been divided into four main chapters. The introduction, or first chapter, deals with the genesis and evolution of some of the concepts pertinent to this work, while the review of the literature is given at the beginning of chapters II and III. The conclusions and claims of originality are summarized in chapter IV.

The option provided by section 7 of the guidelines concerning thesis preparation has been utilized; thus the experimental work of chapter II has already been published in the Journal of Applied Physiology in part (40:417, 1976; Ibid 43:32, 1977) and partly in the American Review of Respiratory Disease (116:457, 1977). Similarly experiment 1 of chapter III has appeared in the Journal of Applied Physiology (43:189, 1977), in addition, the second experiment has been submitted for publication to the same journal. All of these papers are included in this thesis with minor changes.

The units of measurement in this work are those currently employed in the above mentioned journals, and cross reference to the International System of Units (S.I.) is given in Appendix I. Appendix II is comprised of the list of abreviations used in the text of this thesis.

CHAPTER I

INTRODUCTION AND HISTORICAL REVIEW

Οὕτως ἔοικε πάντη χαλεπόν εἶναι καί δυσθήρατον ἱστορίᾳ τἀληθές, ὅταν οἱ μέν ὕστερον γεγονότες τόν χρόνον ἔχωσιν ἐπιπροσθοῦντα τῇ γνώσει τῶν πραγμάτων,ἡ δέ τῶν πράξεων καί τῶν βίων ἡλικιῶτις ἱστορία τά μέν φθόνοις καί δυσμενείαις, τά δέ χαριζομένη καί κολακεύουσα λυμαίνηται καί διαστρέφῃ τήν ἀλήθειαν

Πλούταρχος

To such degree, it seems, is truth hedged about with difficulty and hard to capture by history, since those who come after the events in question find that lapse of time is an obstacle of their proper perception of them; while the research of their contemporaries into men's deeds and lives, partly through envious hatred and partly through fawning flattery, defiles and distorts the truth.

Plutarch

I. 1) From Fiction to Fact

Ancient Greeks regarded the diaphragm as the seat of the soul which they called 'phrenes', a word whose etymology is not clearly known. However, for centuries 'phrenes' meant 'soul' or 'mind'. Homer (1,2) stated that the spirit of life was seated in the diaphragm, while Plato (3) and Aristotle (4) (although considering the diaphragm as part of the soul) attempted to assign to it a more specific function in that part of the body dealing with the psyche. Aristotle (4) wrote in his work "On the Parts of Animals": "This (diaphragm) divides off the heart and lungs and is called 'phrenes' in sanguinous animals.... for they require it to divide the region of the heart from that of the stomach so that the center, wherein abides the sensory soul, may be undisturbed and not be overwhelmed directly when food is taken, by its upstreaming vapor...". The metaphysical aspects of the diaphragm bothered scientists and philosophers until the Renaissance, at which time its anatomy and physiology were greatly investigated.

Hippocrates (5) had already tried clearly and dogmatically to end the myths by stating: "The diaphragm has a name due merely to chance and custom not to reality and nature.I do not know what power the diaphragm has for thought and intelligence. It can only be said that, if a man be unexpectedly overjoyed or grieved, the diaphragm jumps and causes him to start.... since it perceives nothing before the other parts do, but is idly named as though it were the

cause of perception; just like the parts by the heart called 'ears' (auricles), though they contribute nothing to hearing". Six centuries later, the other famous Greek physician and philosopher, Galinos (Galen) from Pergamus of Asia Minor, attributed to the diaphragm the function of respiration. In his work, "De causis respirationis", he wrote: "Of the muscles, the diaphragm is the most useful to the organ of respiration". Galinos cut the intercostal nerves and muscles as well as other inspiratory muscles thus ensuring that the rib cage was relaxed and observed that isolated contraction of the diaphragm expanded the inferior parts of the thorax. In a different series of experiments, Galinos cut both phrenic nerves which resulted in a complete paralysis of the diaphragm while the auxiliary muscles of the upper thorax were instantly set into action (6).

Leonardo da Vinci (7) accurately portrayed the relation of the diaphragm to other organs and Vesalius (8) wrote that the diaphragm "widens the inferior ribs, the sixth and seventh ribs into the cartilages of which it is inserted and it is because of that, that it dilates and increases the capacity of the thorax".

Magendie (9) and Beau and Miassiat (10) subsequently also concluded that the diaphragm lifts the diaphragmatic ribs and displaces them outwards. Duchenne (11), in a rigorous way, also studied the influence of diaphragmatic contraction on the rib cage by stimulating the phrenic nerves in animals and

man. He experimentally produced an expansion of the transverse and antero-posterior diameter of the rib cage. Since then, the inflating action of the diaphragm was studied extensively and its action is elegantly elaborated in the work of Goldman and Mead (12). A brief summary of the latter is as follows: When in man, only the diaphragm contracts, it pushes down the viscera and displaces the abdomen outward. It also lifts and expands the rib cage to the extent that abdominal pressure increases. Thus it seems likely that the diaphragm displaces the relaxed rib cage through the agency of abdominal pressure (Pg), while the fall in pleural pressure (Ppl) inflates the lung.

Duchenne (11) also pointed out that in eviscerated animals, phrenic stimulation may produce diaphragmatic contractions which produce expiration rather than inspiration, an action which subsequently has been confirmed by other investigators (13,14,15,16). This is the case when the diaphragmatic dome is low and the fibers are directed centrally rather than in a cephalad direction. Contraction of the diaphragm under these circumstances tends to pull the lower part of the rib cage inwards. This is likely to be the case at high lung volumes such as in normal subjects near TLC and hyperinflated patients (Hoover's sign).

The intercostal muscles have greatly attracted the attention of investigators throughout medical history. However, the role and function of the intercostals have been a source of controversy. Galinos (6) tightened the intercostal nerves with threads in animals and noticed that the animals were

unable to utter any cries and the movements of the ribs were largely decreased. When he subsequently loosened all the strings, the respiratory movements of the ribs returned and the animals recovered their voices. Since his experiments, the specific actions of the external and internal intercostals have been wholly disputed (10,11,17,18) and only recently was the issue largely resolved by Taylor (19) and Tokizane et al (20) using bipolar needle electrodes. With this technique, it was found that in healthy subjects the external intercostal muscles contract during inspiration. Thus they are called inspiratory, whereas the internal intercostals contract during expiration and they are called expiratory, except for the parasternal intercartilaginous muscles which are inspiratory.

Of all the other muscles which are generally thought to act as accessory muscles of inspiration, only the scaleni and sternocleidomastoids show significant activity in man (21). The abdominal muscles normally are considered as expiratory muscles (21). However, Grimby, Goldman and Mead (22) have emphasized that these muscles may play an inspiratory role as well. The rationale for this being that if the increase in Pg with abdominal muscle contraction inflates the rib cage in the same way that the diaphragm inflates the rib cage through the abdominal pressure, then it is conceivable that abdominal muscle contraction might inflate the lung.

If one were to inspire entirely with the intercostal and accessory muscles keeping the diaphragm and

abdominal muscle relaxed, transdiaphragmatic pressure (Pdi) would be zero and abdominal pressure would be equal to pleural pressure until the diaphragm developed a passive tension. Thus, with each inspiration the fall in Ppl would not only expand the lung but also suck in the abdomen which would oppose the inflation of the lung. It is clear that breathing in this way is most inefficient (22,23,24).

Although the isolated inspiratory action of the diaphragm and intercostals is clearly understood today, the interaction of both of them is the source of a lively controversy between Goldman, Mead and their associates (12,22,24) and Macklem, myself and our colleagues (25). Macklem et al (25) maintain that if the diaphragm contracts isometrically, it cannot perform any external work and all the work along with the pressures necessary to perform it must be developed by intercostal/accessory muscles (Pic). For example, when the abdominal pressure remains unchanged and the abdominal muscles remain relaxed, Macklem et al (25) argue that the diaphragm contracts quasi-isometrically and thus Pic is the total pressure developed across the rib cage pathway, that is, it has supplied the pressure necessary both to inflate the lung and displace the rib cage. The diaphragm has contracted, however, and in such a breath Pdi equals the pressure required to inflate the lung and thus the sum of Pdi and Pic is greater than the total pressure developed across the lungs and rib cage. It follows in Macklem et al's approach that because the diaphragm has performed no work, the diaphragm is acting

as a fixator preventing the transmission of Ppl in the abdomen, and expiratory inward abdominal displacement that would result In contrast, Goldman and Mead's analysis considers the diaphragm always acting as an agonist. All of the pressure developed by the diaphragm at its pleural surface contributes to the inflation of the lung and performs external work. Thus, under the circumstances of an inspiration with the abdominal muscles relaxed and no change in P_g, they conclude that the diaphragm has produced the pressure to inflate the lung, while the intercostal/accessory muscles have produced the pressure to displace the rib cage. The sum of Pdi and Pic thus equals the pressures developed across rib cage and lung. Predictably, following one or the other approach in calculating the work performed by the diaphragm and intercostals, will give different results.

I. 2) Topographical Gas Distribution and Physiotherapy

Davy, in 1800 (26), using hydrogen in a closed lung-spirometer system was the first to investigate the distribution of gas within the lung. He concluded that respiration produced a uniform mixture of residual gas with the gas inspired. The earliest direct method of obtaining information about the function of a region of the lungs consisted of inserting a tube into the bronchus. Such an attempt was undertaken first by Wolffberg, in 1871 (27), using a catheter with two concentric tubes and subsequently by Bernard (28) and Head (29).

Keith, in 1909 (30), stated that the lungs during inspiration do not expand equally like a rubber bag, but expand in a regulated manner, like the opening of a Japanese fan. He defined "root", "intermediate" and "outer" zones of the lung. Differences in topographical distribution were also maintained by Rauwerda (31) who thought that the basal, lateral and frontal parts of the lung were better ventilated than the apical, mediastinal and hilar parts. In 1932, Kwiet (32) showed that the basal lung regions expand more than the apical ones over the vital capacity range. His work was based on the comparison of chest X-rays taken under identical conditions at both residual volume and at total lung capacity. He quantitated the densitometric changes in each radiography along lines spanning from the apex to the base of the lung.

The influence of selective use of the respiratory muscles on ventilation distribution appeared early in this century when Wenckenback (33) claimed that diaphragmatic motion mainly ventilates portions of the lung which are within the area of the paravertebral gutter and close to the hilum. Since then, breathing exercises have been advocated as a therapeutic tool in patients with respiratory insufficiency and Hofbauer (34) introduced diaphragmatic breathing in chronic obstructive pulmonary disease patients.

The first systematic clinical study of breathing exercises was that of Livingston and Gillespie (35) who claimed improvement in some patients with allergic or bronchitic asthma. Miller (36) introduced diaphragmatic

breathing training for three months to patients with chronic airways obstruction and reported improvement in pulmonary function tests including blood gases. However, Sinclair (37) in a similar study did not find any difference. Barach and Dulfano (38) introduced, in addition to the diaphragmatic exercises, leaning the upper body forward to relax the accessory respiratory muscles of the neck and reported decreased minute ventilation and respiratory rate with an increase in tidal volume. Similar findings were reported by Petty and Guthrie (39) by introducing various augmented breathing maneuvers. Campbell and Friend (40), by monitoring the abdominal and accessory muscle activity, lung volumes, and distribution of ventilation, found that during the period of exercise, the poorly ventilated regions were not influenced. The authors concluded that "The breathing exercises produced no effect upon ventilatory function". A lack of beneficial effects has been reported by other workers as well (41) who studied breathing exercises by comparing their effect on patients with chronic airways obstruction to the effect observed in a control group of patients.

The major advance in the investigation of the topographical distribution of ventilation was the introduction of radioactive tracer gases by Knipping et al (42). Thus, the first quantitative measurement of ventilation distribution with radioactive gas was reported by West and Dollery (43) using radioactive ^{15}O and subsequently by Ball et al (44) and Dollfuss et al (45) using radioactive ^{133}Xe. The ^{133}Xe technique has proven very fruitful in understanding the topo-

graphical distribution of ventilation and the studies over the last ten years on the topography of regional lung volumes and distribution of inspired gas, are based on these techniques. They will be discussed in detail in the next chapter.

I. 3) Respiratory Muscles as a Failing Pump

In 1901, Rehns (46) observed that after injecting a soluble salt of paraphenylenediamine into mice, the diaphragm oxidized the salt and remained black for life, while almost all the other muscles had to be exposed to "oxygène d'atmosphère" in order to oxidize the salt. Based on these observations, Rehns concluded that the diaphragm is peculiar among muscles regarding its ability to possess a superabundant supply of oxygen. Furthermore, Rehns attributed to this property, the resistance of the diaphragm to be paralyzed by curare and its ability to maintain its contractility longer than the other muscles. Lee et al,in 1916 (47) performed a comparative study of several physiological properties of four skeletal muscles of the cat (diaphragm, extensor longus digitorum, sartorius and soleus) and concluded that "the diaphragm to most of the properties stands by itself in the lead of all the others; a peculiarity that is not yet explained, but may possibly be associated with the greater power of the diaphragm to utilize oxygen". In the work of Lee et al (47), it was found that the diaphragm was less deleteriously affected when the body was subjected to high heat and high humidity, submitted last to the action of curare, worked for a longer

period and accomplished more work per cross-sectional area than any of the other muscles receiving the same stimulus. It was superior in absolute power, and by extreme inanition, the total working period of the excised diaphragm was shortened far less than the others.

Davies, Haldane and Priestley (48) pointed out that breathing through excessive resistance may lead to fatigue of the central control system of respiration. The occurrence of fatigue, according to these authors, is responsible for the fast shallow breathing observed towards the end of a run, after breathing through resistances. The same authors tested the influence of breathing 10.2% oxygen in the inspired gas, and they found that the "onset" of fatigue and consequent shallowness of respiration was very rapid and sudden. The authors were fascinated by their findings, and they stated: "The phenomena in question are of great importance in practical medicine. They throw quite a new light on failure of the respiratory centre as a common perhaps the commonest immediate cause of death...". Six years later,Davies, Brow and Binger (49) brought up, for the first time in respiratory medicine, the possibility of respiratory muscle fatigue. The authors measured ventilation during successive periods of rebreathing and found that ventilation fell after several rebreathing tests at high CO_2 percentages and increased at low CO_2 percentages. Based on these observations, Davies et al suggested that the respiratory fatigue consists of twc elements: 1) neural, manifesting itself in increased excitability of the respiratory

center and a more marked response to a normal stimulus when the demand for pulmonary ventilation is small and 2) muscular, where the muscles of respiration are unable to respond adequately when the demand for pulmonary ventilation is high. Similar conclusions were drawn later by Killick (50) when she studied the effect of inspiratory resistances in man.

The question, whether the respiratory muscles may fatigue and be responsible in cases of respiratory failure, has been asked since the beginning of the century, time and time again. Yet, few studies have appeared attempting to answer the question and those that have, have only been published in the last 15 years. One of the objects in these studies was to determine under normocapnic conditions the level of ventilation below which subjects could breathe indefinitely. Zocche et al, in 1960 (51), found that normal subjects were capable of maintaining a ventilatory level of 53% of maximum voluntary ventilation (MVV) for 15 minutes while Tenney and Reese, later in 1968 (52), and Freedman, in 1970 (53), estimated the ventilation that can be maintained more or less indefinitely to be 50-55% of MVV. On the other hand, Shephard (54) and most recently Leith and Bradley (55) found that normal subjects could ventilate at 70-80% of MVV for 15 minutes. No obvious reason can explain the discrepancy in the various studies but the inconsistency could be related to differences in respiratory rate and depth in the different studies. Apart from these few studies, I have been unable to find any reports in the literature describing loads

sufficient to cause respiratory muscle fatigue in either normal subjects or patients.

CHAPTER II

VENTILATION DISTRIBUTION

Πνεῦμα δέ τό μέν ἐν τοῖσι σώμασι
φῦσα καλεῖται,
τό δέ ἔξω τῶν σωμάτων ὁ ἀήρ.

Ἱπποκράτης

Wind in bodies is called
breath,
Outside bodies it is called
air.

Hippocrates

II. 1. Review of the Literature

II. 1. 1) Regional and Overall Lung Volumes

It was only in 1966 that the first clear evidence appeared that there is a vertical gradient in alveolar size. Milic-Emili et al (56), Kaneko et al (57) and Sutherland et al (58) using radioactive ^{133}Xe, demonstrated that at all overall lung volumes except at total lung capacity where the alveolar size was assumed to be equal, the nondependent lung regions are more expanded than the dependent ones. On the contrary, no significant differences were found among lung regions in the same horizontal plane both in the upright and in the horizontal postures (56,57,59,60). The magnitude of the vertical lung volume gradient bears some relation to body posture. Milic-Emili (61) has reported more uniform vertical lung expansion in the head-down position than in the upright position. Furthermore, Kaneko et al (57) showed slightly greater vertical lung expansion in the lateral posture compared to prone or supine postures.

Confirmation for the existence of the vertical gradient of the lung expansion was obtained later by freezing whole dogs. Glazier et al (62), using morphometric techniques, found a significant alveolar size gradient at FRC in head-up frozen dogs. Measuring the lung density, Hogg and Nepszy (63) also confirmed the vertical gradient of lung expansion. The only contradictory finding is cited in the study by Glazier et al (62) where it was found that the alveoli of the lung apices in head-up dogs were smaller at

an inflating pressure of 30 cmH_2O, compared to their size at functional residual capacity. However, these findings were neither confirmed by Hogg and Nepszy (63) nor by D'Angelo (64). Small pneumothoraces at the apices due to the inflating pressure of 30 cmH_2O that Glazier et al (62) applied, may account for this paradox. The morphometric studies of Glazier et al at high inflating pressure (30 cmH_2O) confirmed another prediction of Milic-Emili et al (56) regarding the alveolar size at TLC. That is, for the exception of the apical alveoli, the rest of the lung was uniformly expanded.

From the work of Sutherland et al (58) the vertical gradient of alveolar expansion seems to be unaffected by the previous volume history. In the work of Milic-Emili et al (56) and Kaneko et al (57), this gradient is practically linear for lung volumes above 46% TLC while for lower lung volumes it is alinear. The alinearity was attributed to the airway closure of the dependent lung regions. Burger and Macklem (65) and Engel et al (66) subsequently produced strong evidence in favour of closure.

II. 1. 2) Topography of Pleural Pressure

An early attempt to measure directly the pleural pressure (Ppl) in man was conducted by Parodi in 1933 (67) producing small pneumothoraces. Similar approaches were undertaken later by Prinzmetal and Kountz (68) and Daly and Bondurant (69). They observed that the nondependent lung regions were surrounded by more negative Ppl than the

dependent ones. The vertical pleural pressure gradient (dPpl/dD) was subsequently investigated both in humans and animals using different techniques. Krueger et al (70) using a small balloon in the pleural space in head-up dogs, found a vertical gradient of end expiratory pleural pressure, approximately 0.21 cmH_2O/cm height. MacMahon et al (71) by the means of Starling resistors found in dogs a gradient of 0.20 cmH_2O/cm in the head-up posture and 0.31 cmH_2O/cm in the head-down posture. Hoppin et al (72) using multiple flat balloons found a top to bottom gradient of 0.30 cmH_2O/cm. The most systematic exploration regarding the topography of the pleural pressure in animals was undertaken by Agostoni, D'Angelo, Miserocchi and their co-workers using the counter pressure technique that they developed (73,74,75,76,77).

One of the great advantages of this technique was that it made feasible the simultaneous measurements over most of the intercostal and diaphragmatic regions without separating the two pleural surfaces. The existence of the pleural pressure gradient was repeatedly confirmed in their work using dogs, rabbits, rats and rams as experimental animals. Important conclusions that may be drawn from their work are: 1) the overall dPpl/dD decreases as the size of the animal increases (73), 2) the dPpl/dD in lateral posture is greater than in other postures(73,78); for example, in small dogs being 0.82 cmH_2O/cm in lateral compared to 0.45 cmH_2O/cm in head-up position, 3) when the respiratory system was expanded by the action of its muscles up to at least 10-12 cmH_2O

transpulmonary pressure, the dPpl/dD at the end of inspiration was not significantly different from that at the end of expiration; in contrast, when the relaxed respiratory system was artificially expanded, the dPpl/dD decreased and eventually became nil in supine and head-up postures (76,77), 4) at a given height in the cranio-caudal direction, in supine posture, no systematic difference in pleural surface pressure was found (77), 5) gravity affects the topography of pleural pressure mainly by acting on the chest wall, the shape of which is changed (74,75).

Parodi, in 1933 (67), reported in man the uniformity of pleural pressure at the same horizontal plane. Similar conclusions were later drawn indirectly using radioactive ^{133}Xe in man (56, 57). Furthermore, the same investigators computed the relationship between lung height and pleural surface pressure at different postures. This was achieved on the principle that the regional distribution of the pleural pressure can be derived by assuming that the elastic properties of each region were identical, and by knowing the static pressure-volume characteristics of the whole lung and the static regional distribution of volumes. Thus, Milic-Emili et al (56) found an average gradient of 0.20 cmH_2O/cm in upright man and Kaneko et al (57) found a vertical pressure gradient ranging from 0.16 to 0.18 cmH_2O in prone, supine and lateral postures.

II. 1. 3) Relationship of Regional Lung Volume and Pleural Pressure

In 1972, D'Angelo (64) measured local alveolar size and transpulmonary pressure in intact rabbits and in isolated rabbit lungs. In his elegant work, D'Angelo demonstrated that in a variety of conditions all his measurements in situ fit the pressure-volume (V-P) relationship of the isolated lung. He also demonstrated that the geometry of alveoli in situ was very similar to that observed in the isolated lung. Thus, D'Angelo demonstrated in his work that the relationship between alveolar size,geometry and transpulmonary pressure (P_L) remains unique for each lung lobe tested both in isolated and in situ lung preparation.

In man, Sutherland et al (58) in 1968 related regional lung volume measured by the ^{133}Xe technique to local transpulmonary pressure using the esophageal balloon technique (79,80). In this work it was shown that all lung regions (upper,middle and lower) have similar volume-pressure relationships at least during expiration. However, the results of Bake et al (60) who studied the regional distribution on inspired gas in supine man, do not support the notion that all lung lobes have the same intrinsic static mechanical properties. They argue that there may be differences in human upper and lower lobes similar to that observed in rabbits (64) and dogs (81). Definite conclusions from this study, however, cannot be drawn because the number of subjects is small, and there may be substantial interindividual differences.

II. 1. 4) Quasi-static Distribution of Inspired Gas.

The distribution of inspired gas can be explained with a simple mechanical model proposed by Milic-Emili (61) accepting two premises: a) that the elastic properties of the lung are uniform, and b) that the dPpl/dD remains constant. It is implicit that a constant dPpl/dD necessitates equal changes of Ppl with changes in lung volume. Thus, all regions in the same horizontal plane are expanded to the same degree whereas vertically distributed regions exhibit a gradient of expansion corresponding to the vertical gradient of transpulmonary pressure. During slow inspiration, when all airways are open, the lower lung regions operate on a steeper part of the static volume-pressure curve because they are less expanded than the upper lung regions. Thus, for the same change of Ppl they must receive more ventilation. In this way, the distribution of the gas may be accounted for by the distribution of regional pulmonary compliance. It follows that the distribution of ventilation tends to be preferential to the dependent lung zones. A different situation pertains during an inspiration which commences from residual volume. In this case, the bottom of the lung with the closed airway receives none of the inspired gas until the closed airways reopen. Under these conditions the inhaled gas is preferentially distributed to the nondependent lung units.

In the described model, it is evident that for lung volumes above the closing volume, filling and emptying of all

lung regions is uniform. In reality, however, this is not the case. Dependent regions are seen to empty preferentially at higher lung volumes and this sequential emptying is gravity dependent (82). Three mechanisms proposed by Sutherland et al (58) may explain this fact: 1) differences in lobar volume-pressure (V-P) curves; however, in the prone posture in man where the upper lobes are located below the lower lobes the gravity dependent sequential emptying still remains, 2) nonmonoexponential V-P curve of the lung, as was proposed by Paiva et al (83), in contrast to a single exponential curve proposed by others (84, 85), 3) regional differences in applied pleural pressure; during an expiration greater changes of applied pressure over the dependent lung regions at high lung volumes and over the nondependent regions at low lung volumes will result in sequential emptying. This notion will be extensively discussed in the subsequent section and it will be an important concept in my work on the influence of the action of the respiratory muscles on ventilation distribution.

II. 1. 5) Influence of Respiratory Muscle Action on the Topography of Pleural Pressure and Regional Gas Distribution

Contraction of the respiratory muscles may alter both the dimensions and the shape of the chest wall. If the thorax were filled with liquid, the dPpl/dD would remain constant and the pressure swings would be everywhere equal, regardless of the shape of the chest wall.

However, a material resistant to deformation may affect the gradient, the pressure swings and, therefore, regional alveolar size and ventilation. The real situation is complex and great controversy exists in the literature regarding the nature of the pleural pressure gradient.

First, Wirz in 1923 (86), later Rohrer in 1925 (87), and then Parodi in 1933 (67), pointed out that the weight of the lung can produce a gradient of transpulmonary pressure. Krueger et al, in 1961 (70), having found that the lung density is 0.22 gr/ml which is very close to the overall gradient of the transpulmonary pressure, hypothesized that the lung behaves as a homogeneous fluid so that the pleural pressure gradient was hydrostatic and was the result of the effect of gravity on the thoracic contents.

The hypothesis that the lung behaves like a liquid was also advocated by Milic-Emili and his coworkers (56). They based their reasoning on two findings: 1) the transpulmonary gradient that they found was similar to the lung density reported by Krueger et al (70) and 2) the transpulmonary pressure gradient increased with acceleration and became nil if the data were extrapolated to zero (88). Similar approaches were taken by Proctor et al (89) and Glaister (90,91).

Vawter et al (92), working on a theoretical model of the lung by using finite element analysis of a homogeneous isotropic material, concluded that the weight of the lung is the major determinant of the regional differences in

pleural pressure. The investigators predicted, however, that the lung will have a vertical gradient of alveolar size when the lung is assumed to be supported at its periphery inside a container, the chest wall. However, experimental findings failed to prove the validity of this prediction. Excised lungs supported by the base or by the apex show no such gradient (93). Vawter et al (92) also predicted that differences between apex and base are directly proportional to the height of the lung. This also did not prove to be the case among species of different sizes (73). On the other hand,the prediction that at zero gravity the transpulmonary pressure gradient will be abolished was recently confirmed during short periods of zero gravity (94). However, one may argue that the effect of gravity in this study was eliminated mainly from the chest wall whose shape might have been altered sufficiently to abolish the gradient.

In 1954, Duomarco et al (95) and later Mead in 1961 (96), and Turner in 1962 (97) considered that besides the lung weight, differences in the shape of the lung and of the chest wall could be responsible for regional differences of transpulmonary pressure. Hoppin et al (72) tested the influence of shape changes in dogs at FRC and they concluded that the gradient may be relatively independent of the chest wall shape. The same authors, however, found that at high lung volumes, the vertical gradient significantly decreases. Thus, Hoppin et al (72) and Mead (98) maintained that at low and middle lung volumes, the lung behaves almost as a liquid, whereas at high lung volumes resistance to shear

of the lung tissue is marked and the lung behaves less like a liquid.

Agostoni, D'Angelo and their coworkers have provided impressive evidence that mismatching of the shape of the lung and chest wall is the most important cause of the topography of the pleural pressure in animals. Furthermore, they claim that although gravity affects the dPpl/dD, this occurs via the change of the chest wall shape. Agostoni et al (74) determined the topography of pleural surface pressure after evisceration and compared their results with those obtained under normal conditions. Their results showed that the gradient decreased. This effect was particularly marked in the horizontal posture. They concluded that this phenomenon was due to the vertical gradient of abdominal pressure. D'Angelo et al (99) measured the pleural surface pressure at various heights in rabbits after changing the lung weight, eviscerating the animals, and removing the diaphragm. Exsanguination produced a decrease in lung weight but the dPpl/dD remained unchanged, whereas evisceration and removal of the diaphragm decreased the dPpl/dD. The authors argued that removal of the diaphragm abolished the interaction between diaphragm and rib cage which consequently produced changes in chest wall shape. However, even after removal of the diaphragm a dPpl/dD still persisted. To evaluate the degree that the lung weight contributes to this gradient, D'Angelo et al (99) performed the same experiments in prone suspended posture. The

rationale of this experiment was that if the gradient of pleural pressure which remained after the removal of the diaphragm were due to the shape in the supine posture, then in the prone suspended position this residual gradient should be the reverse of that observed in the supine. In fact, it was the same. They concluded that this residual pleural pressure gradient was due to the lung weight and accounted for 20-25% of the total gradient. In their work, they postulated that the effect of gravity on the chest wall remained essentially the same in the supine and the prone postures. However, such an assumption may not be correct in small animals with very distortable rib cages. If this were the case, the proportion attributable to the lung weight might be even less.

Predictably, altering the shape of the chest wall or modifying the effect of gravity in the chest wall will also change the topography of the pleural pressure. Agostoni and his coworkers undertook impressively convincing experimental work in animals along these lines (75,100,101). An important finding was that by altering the effect of gravity on the chest wall shape, the pleural surface pressure in the costal region may be markedly different at a given height and in a given posture. Agostoni and D'Angelo (75) decreased the pressure over the caudal part of the abdomen of supine rabbits and dogs at FRC, and found that the pleural surface pressure in the cranial region decreased more than in the caudal, at the same horizontal plane. Thus, a craniocaudal gradient was produced similar to the one in the head-up posi-

tion. In the same experiments, in head-down posture, when the abdominal pressure was decreased to such an extent as to increase the lung volume as in the head-up posture at FRC, the vertical gradient was reversed and it became almost equal to that in the head-up posture at FRC. Furthermore, Agostoni et al (74) determined the distribution of Ppl after evisceration and compared these data with those obtained under normal conditions. It was found that the dPpl/dD decreased markedly after evisceration. D'Angelo and Agostoni (102) examined also the effect of lung stiffness on the pleural pressure distribution, the notion being that the stiffer the lung the greater its resistance to distortion and consequently the matching of lung and chest wall shape will require greater pressures. Their experiments fulfilled their prediction. They found increased gradient both in the upright and the supine postures after histamine inhalation. Thus, these experimental findings contradict the prediction of West and Matthews (103) from their finite element model analysis, that if the gradient were due to the weight of the lung it would become smaller with increased lung stiffness.

Greene et al (104) studied the effect of gravity on the chest wall in seated man immersed up to the xiphoid and in air, at matched lung volumes, namely FRC and 73% TLC. The rationale was that immersion in water would eliminate the effect of abdominal weight. The latter might alter the chest wall shape and consequently the distribution of lung volume, without affecting the lung weight. Their findings did not support the experimental conclusions in animals.

In fact, they did not find any differences in the two conditions. Thus, this study brings up the possibility that a difference exists between humans and animals, as far as the effect of gravity on dPpl/dD is concerned. However, a difference in behaviour between animals and man was reported earlier by Lemelin et al (105). They found that, in man, the vertical gradient of regional lung volumes was not abolished as it was in animals (76), when the respiratory system was passively expanded. Further substantiation of the difference between man and small animals regarding the influence of chest wall shape on the regional lung volumes and pleural pressure was offered by Grassino et al (106) and Bake et al (107). They showed that varying the volume distribution between rib cage and abdomen by voluntary shape changes of the chest wall, had no effect on regional lung volume distribution. Furthermore, Grassino and Anthonisen (108) showed that application of negative pressure on the human abdomen in the supine posture did not affect the apicocaudal regional lung volume distribution. This was in contrast to the finding of Agostoni and D'Angelo in animals (75). Grassino and Anthonisen, however, were able to produce regional differences in lung volume when the respiratory system was distorted by strong lateral compression of the lower rib cage (108). Grassino et al (106) attributed these results to the differences in rib cage compliance between man and small animals. In fact, they provided some evidence that such is the case, by showing that the rib cage in humans is more rigid and behaves in a homogeneous manner.

They measured the change in cross-sectional areas of the rib cage at different levels and found that it decreased or increased by the same percentage during their maneuvers (belly-in, belly-out) or when they applied negative pressure on the abdomen. In contrast, Agostoni and D'Angelo (75) showed that application of negative pressure on the abdomen in supine rabbits produces a greater decrease of the cross-sectional area of the caudal part of the rib cage than that of the cranial part.

It becomes apparent that, in man, the changes in shape of the chest wall of the magnitude created by Grassino et al (106) do not have as striking an effect as in small animals. To stir up the issue more, Grassino and Anthonisen (109) performed an extremely important experiment in which they measured the thoracoabdominal configuration and regional lung volumes at FRC during increased gravity in seated man. They reported minor changes in the rib cage and abdominal configuration with small decreases in A-P diameter and increases in the lateral diameter of the rib cage and abdomen, whereas the vertical gradient of the regional lung volumes markedly increased. In contrast, during Mueller like maneuvers, they found similar changes in chest wall shape but opposite effects on the vertical gradient of regional lung volumes. Therefore, from the experiments of Grassino and his coworkers (106,108,109), it follows that both the shape of the chest wall and the weight of the lung can be important on the distribution of the lung volumes and probably

the net effect is the relative magnitude between them.

An important question that remains to be examined is whether the respiratory muscles can significantly alter the shape of the chest wall configuration and consequently the regional lung volumes and pleural pressure or the distribution of inspired gas. D'Angelo et al (110) showed in animals that phrenic nerve stimulation in dogs caused a greater change in the Ppl in the lower intercostal spaces than in the upper intercostal spaces. In fact, the greatest change was recorded over the diaphragmatic surface. In contrast, after phrenicotomy, the swings in pleural pressure were greater in the upper than in the lower interspaces which were in turn greater than those measured over the diaphragmatic area. They concluded that "the greater changes in pressure are localized where the respiratory muscles act". Minh et al (111) independently measured the changes in dPpl/dD in head-up dogs during bilateral phrenic stimulation and found that dPpl/dD became reversed. Furthermore, they observed that the apicobasal lung dimension increased whereas the lateral dimensions decreased. Similarly, in supine posture, they found that ipsilateral phrenic stimulation produced greater changes in Ppl over the basal than over the apical zones. This seemed to imply that, in dogs, selective contraction of the diaphragm may result in greater basal ventilation, a prediction that was not confirmed by the same investigators (112). In these experiments, Minh et al (112) measured the alveolar ventilation ($\dot{V}_A$), dead space (V_D) and dead space to tidal breath ratio (V_D/V_T) after they ligated the lower and middle lobe

pulmonary arteries, under two conditions: 1) during bilateral electrophrenic respiration and 2) during positive pressure assisted ventilation. In the former case, both A-P and lateral diameters of the rib cage decreased at all levels of thoracic vertebrae whereas the thoracic cephalocaudal dimension greatly increased. In the latter case, all dimensions increased. Despite the great differences in configuration between the two conditions, no differences were found in $\dot{V}_A$, V_D, and V_D/V_T. The authors explained their results due to lobar interdependence. "The preferential expansion of the base of the chest results in an inflation of the lower lobes. With the lower lobes inflated , the pleural pressure surrounding it (facing the rib cage as well as the interlobar tissue) increases in negativity. Exposed to more negative Ppl at the interlobar tissue, the middle lobes inflate. By a similar mechanism the upper lobes inflate from the increase in negativity of the Ppl in the interlobar tissue facing the middle lobe...". However, this explanation contradicts their finding during phrenic stimulation. Should this interpretation be correct, they should not have found greater changes in Ppl over basal compared to apical regions (111).

In man, selective contraction of the respiratory muscles produceschanges in the dPpl/dD similar to those observed in animals (113). It was shown in this work that the esophageal pressure gradient in upright man is enhanced during Mueller maneuvers performed mainly with the intercostal accessory muscles, whereas similar efforts produced by diaphragmatic contraction resulted in little change or had the

opposite effect. Indirect evidence that the ventilation of the inspired gas may be directed selectively to different lung regions, is found in the work of Froese and Bryan (114). They reported that during spontaneous breathing in the horizontal posture, diaphragmatic motion was greater over the dependent regions whereas in anesthetized paralyzed subjects who were artificially ventilated, diaphragmatic motion was greater over the nondependent region. These observations indicate that diaphragmatic tone may affect regional lung ventilation. The contraction and relaxation, preferential probably in the lower part during breathing, may produce greater pleural pressure swings in the lower lung regions and therefore greater ventilation in the dependent lung. Direct measurements in spontaneous breathing supine dogs by Farhi et al (115) indeed showed that the pleural pressure swings were greater in the diaphragmatic sinus at the posterior vertebral sulcus than they were at other sites over the costal surface of the lung. However, there is no evidence in the literature that at FRC, breathing exercise alters the distribution of inspired gas either in normal subjects or in patients with obstructive pulmonary disease (107, 116, 117, 118, 119). The only report that mentions preferential distribution of the inspired gas towards the bottom of the lung during "diaphragmatic" type breathing starting at residual volume is by Sackner et al (117) in which five out of eight normal subjects were tested. They measured the topographical distribution of a bolus of ^{133}Xe (5 ml of air containing 10-15 mCi ^{133}Xe) inspired at residual lung volume. However,

the authors do not provide any direct experimental evidence that the subjects commenced their inspiration from residual volume. An inspiration commencing above residual volume in these subjects may account for the preferential distribution of the bases.

II. 2. Experiments

II. 2. 1) Diaphragmatic Contraction and Vertical Lung Expansion in Horizontal Man

a) Summary

Using ^{133}Xe we measured the vertical distribution of regional volume in four subjects in the lateral decubitus posture at 20, 40, 60 and 80% of vital capacity (VC), when transdiaphragmatic pressure (Pdi) was low (RD = 'relaxed' diaphragm) or during voluntary diaphragmatic contraction (VDC) achieved without changing lung volume by simultaneously tensing the abdominal muscles. Under both conditions the gradient of alveolar expansion tended to be curvilinear, and in all lung volumes the difference in regional volumes between dependent and nondependent lung regions was less during VDC than during RD. At 70% VC this difference was six fold. In six other subjects the washout of a bolus of helium (inhaled from residual volume) during relaxed expiration (RE) through a resistance was compared with that during expiration with VDC (VDCE) while maintaining constant expiratory flow (0.4 l/s). Phase IV during RE started at 58 ±1.6% vital capacity (VC) (mean ± SE). During VDCE when Pdi exceeded 30 cmH_2O, phase IV commenced at 8.2 ±0.8% VC. The expired He concentration ($F_{E_{He}}$) at lung volumes 70% VC was 1.3 ±0.05 times that during RE. In supine subjects VDCE flattened the slope of the alveolar plateau and decreased closing volume by 3.7 ± 0.4 % VC. In conclusion, diaphragmatic tension decreases the gradient in pleural pressure and regional volumes and produces more homogeneous lung emptying by modi-

fying the transmission of the abdominal hydrostatic pressure gradient to the thorax and, in addition, in lateral posture by an upward displacement of the mediastinum.

b) Introduction

Several observations have led us to question the validity of the assumption that only regional pulmonary compliance determines the distribution of ventilation at low flow rates in the horizontal posture. In particular, Froese and Bryan (114) reported that in subjects in the supine and lateral positions, inspiratory diaphragmatic motion was quite different when breathing spontaneously from that in paralyzed, artificially ventilated subjects. In the former condition, the greater displacement was in the inferior part of the diaphragm; in the latter, it was in the superior part. This suggested that the distribution of ventilation is preferential to lower zones when the diaphragm is contracting, and preferential to upper zones during artificial ventilation when the diaphragm is paralyzed. The authors hypothesized that the relaxed diaphragm transmits the hydrostatic pressure gradient in the abdomen to the pleural surface better than does the contracted diaphragm. We wondered whether in conscious, spontaneously breathing subjects, mild degrees of diaphragmatic tone may not modify the transmission of intra-abdominal pressure to the pleural surface, with resulting changes in diaphragmatic displacement, pleural pressure gradient and ventilation distribution.

To test our hypothesis that in the horizontal subject the vertical gradient of alveolar distention, and hence of pleural pressure, might be influenced by diaphragmatic contraction, we made some preliminary observations. The results of two radiographs, taken at the same lung volume, of a subject in the lateral position with the diaphragm relaxed and with it contracted are shown in Fig. 1. When the subject relaxed, the dependent hemi-diaphragm was more cephalad and the mediastinum encroached more upon the dependent lung than was the case when he contracted the diaphragm. With diaphragmatic contraction, the lower lung inflated and the upper lung deflated. It follows that the contraction increased the mean transpulmonary pressure across the dependent lung and decreased it over the upper lung. Consequently, the vertical difference in alveolar size and pleural pressure must have decreased. Furthermore, if indeed diaphragmatic contraction decreases both the gradient in alveolar size and in pleural pressure, then the washout also of a bolus of tracer gas inhaled at RV should be different when performed with the diaphragm relaxed from that obtained with the diaphragm contracted. In the former case, with a large gradient in pleural pressure, the degree of sequential emptying might be greater and the onset of Phase IV earlier than it would be with the diaphragm contracted.

c) Methods

1) Studies Using ^{133}Xe: Four normal male subjects were studied in the right lateral decubitus posture. The

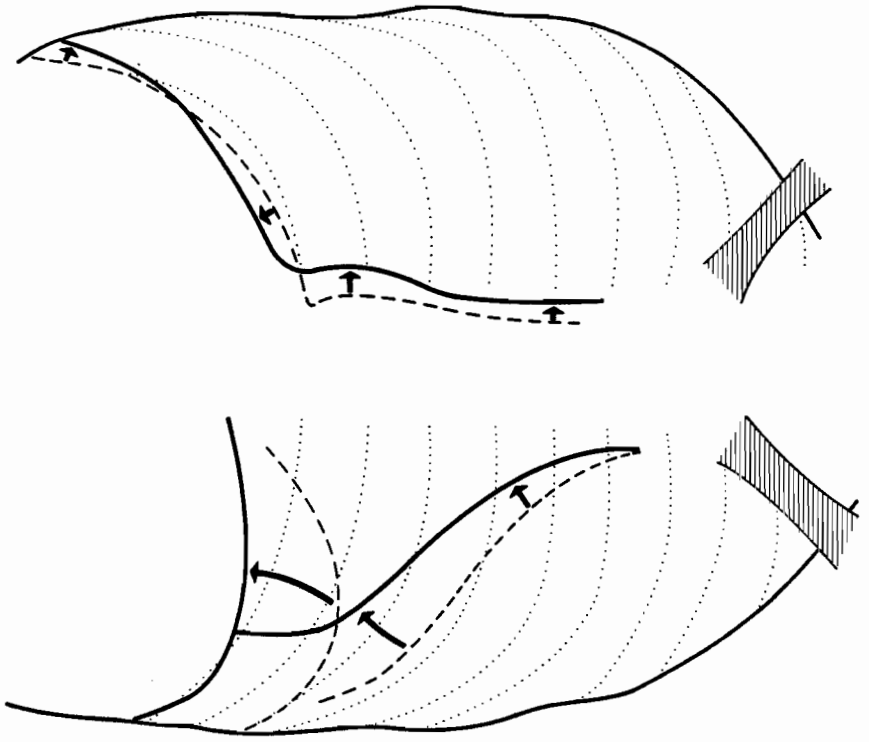

Figure 1: Diagrammatic representation of two chest radiographs at the same lung volume (functional residual capacity, FRC) of a subject in the lateral decubitus position. Broken line: position of the diaphragm and mediastinum with diaphragm relaxed (low transdiaphragmatic pressure, Pdi). Solid line: position of the diaphragm and mediastinum with contracted diaphragm (high Pdi). Arrows show the motion of the diaphragm and mediastinum when the diaphragm is contracted.

distribution of regional volume was measured at four overall lung volumes (approximating 20, 40, 60 and 80% vital capacity , VC) under conditions when the diaphragm was 'relaxed' and when it was voluntarily contracted. The latter was achieved by tensing the abdominal muscles with the glottis open. Each subject performed identical maneuvers (Fig. 2). After breathing quietly at functional residual capacity (FRC), he expired to residual volume, and then inspired to total lung capacity (TLC), in order to achieve a standard volume history. The subsequent part of the maneuver was performed in one of two ways. In one case, the subject contracted his abdominal muscles with the glottis open necessitating the contraction of the diaphragm to maintain lung volume unchanged. Then, while maintaining a high transdiaphragmatic pressure (Pdi), he expired to a predetermined lung volume (approximately 20, 40, 60 or 80% VC) from which he inspired a gas mixture labeled with ^{133}Xe, up to TLC_2 (Fig. 2). Regional count rates were measured during a 10-20 s breathhold at TLC_2. The subject then expired slowly to residual volume (RV) in a natural manner while ^{133} Xe count rates were measured at the mouth.

In the second type of maneuver, after a similar volume history, the subject expired from TLC_1 with the diaphragm 'relaxed' down to the predetermined lung volume. (Fig. 2). He then inspired a ^{133}Xe labeled gas mixture using mainly the intercostal and accessory muscles, so that Pdi did not increase during the inhalation of the first 0.5 liter

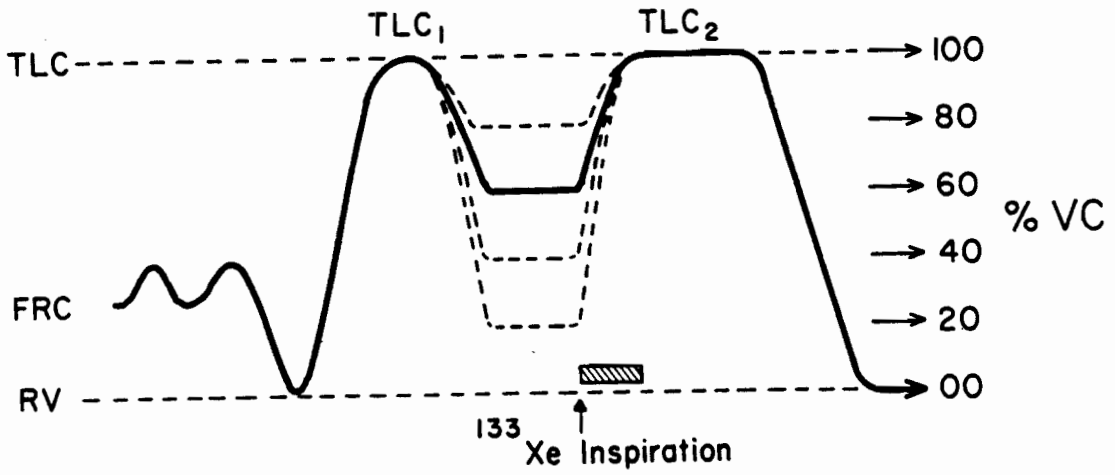

Figure 2: Experimental procedure during each maneuver. Before TLC, volume history was always the same; quiet breathing at FRC, expiration to RV and inspiration to TLC_1. ^{133}Xe labeled gas was inhaled from different lung volumes up to TLC_2. All regional count rates were obtained at TLC_2. See Methods for details.

of ^{133}Xe gas. The remainder of the inspiration to TLC_2 was performed spontaneously and the measurement of regional count rates as well as the subsequent expiration to RV was identical to that during the first type of maneuver. Thus the main difference between the two types of maneuvers was in the degree of contraction of the diaphragm and abdominal muscles during and prior to the inhalation of ^{133}Xe. The two different patterns of deflation from TLC_1 to the volume in question were performed in order to achieve an appropriate volume history for all lung regions prior to each inhalation.

All volume changes were at a rate of less than 0.5 l/s, and the subjects performed the maneuvers aided by a display of Pdi on an oscilloscope in front of them. In addition, each subject was passively inflated with ^{133}Xe-labeled gas from two different lung volumes. The purpose of this maneuver was to test whether a further decrease of Pdi achieved by passive inflation had any effect on regional volume. In fact, the Pdi with passive inflation was 5-10 cm H_2O less than during an inspiration with intercostal and accessory muscles. In some cases the subjects were completely unable to relax the diaphragm during the positive pressure inflation and these maneuvers were rejected. Although Pdi was zero in only one instance, in all passive inflations it was less than during the active 'relaxed' diaphragm inflations.

At each lung volume the inspired ^{133}Xe concentration was adjusted so that the mean ^{133}Xe concentration in the lung at TLC was approximately constant. This facilitated

the comparison of expired ^{133}Xe versus volume curves during the subsequent expiration. All regional count rates were related to corresponding measurements made during equilibration with a known concentration of ^{133}Xe gas (44).

The subjects breathed through a lead-shielded plastic cuvette which contained a scintillation counter and was connected to a two-way tap. The latter could be opened either to room air or to a valved bag-box spirometer circuit. The subjects inspired from the bag and expired into the box, the volume excursion being measured by a spirometer (Stead-Wells). Expired ^{133}Xe concentration was recorded by the counter in the cuvette, which was connected to a digital rate meter whose analog output drove one ordinate of an XYY' recorder. On the abscissa, volume was obtained potentiometrically, while the other ordinate represented expiratory flow rate obtained by differentiating the volume signal.

The regional count rates were measured with 6 pairs of horizontal scintillation counters fitted with 16.5 cm slit lead collimators. The counters were positioned vertically, 5 cm apart, behind the thorax. Thus, the uppermost 2 pairs of counters faced the nondependent (left) lung, the lowermost 2 pairs faced the dependent (right) lung, whereas the mediastinum influenced measurements made by the middle 2 pairs of counters. Skin markings made on the chest of each subject ensured constancy of position during counting at TLC.

Regional volumes were calculated using the method of Milic-Emili et al (56). Data analysis was performed on-line by a computer (Data General) with off-line plotting

of the analog output from each counter.

2) Studies Using Helium (He): Single-breath He washouts were studied in six subjects in the lateral decubitus and supine positions. Each expired to RV and then inhaled 150 ml of He followed by air at a constant flow (0.5 l/s), up to total lung capacity (TLC). The subsequent expiration to RV was performed at a constant low flow rate (0.4 l/s) as follows:

i) Relaxed expiration (RE). The subject controlled expiratory flow with the help of a resistance.

ii) Expiration with voluntary diaphragmatic contraction (VDCE). In this maneuver, the subjects voluntarily contracted their abdominal muscles while keeping expiratory flow constant. This necessitated contraction of the diaphragm to oppose the expiratory effect of abdominal muscle contraction. Transdiaphragmatic pressures (Pdi) were maintained above 30 cmH_2O throughout the expiration.

iii) Expiration with step changes in Pdi. During RE, subjects increased their Pdi abruptly without changing flow, finishing the expiration with the diaphragm contracted. Alternatively, during a VDCE, they decreased the Pdi abruptly, the remainder of the expiration being similar to an RE maneuver. These changes were performed at lung volumes of either 65-80% or 20-55% vital capacity (VC).

Three subjects inhaled a bolus at different lung volumes (15-50% VC), then exhaled from TLC with the diaphragm relaxed (low Pdi).

Each of these maneuvers was executed in the lateral decubitus position at least three times by each subject. Numbers I and II were also studied in five supine subjects.

We sampled the expired gas close to the lips and measured the concentration of He ($F_{E_{He}}$) with a mass spectrometer (Perkin-Elmer). We measured flow rate with a Fleisch pneumotachograph and a Validyne differential pressure transducer whose signal was integrated to measure changes in volumes. The flow and He signals were recorded against volume on the ordinates of an XYY' recorder. The total amount of He expired during each maneuver was calculated by electrically integrating the $F_{E_{He}}$ signal with volume.

3) Pressure Measurements: Transdiaphragmatic pressure was defined as the difference between gastric and esophageal pressures. These were measured by means of two thin-walled latex balloons (5 cm long and 3 cm in circumference), one positioned in the stomach and the other in the middle third of the esophagus. The esophageal balloon was connected by a polyethylene catheter and a Y-tube to one side of each of two pressure transducers (Sanborn 267B), the other sides having attached to them, respectively, the gastric balloon and a catheter that measured mouth pressure. The first transducer recorded Pdi; the second measured transpulmonary pressure. In the upright posture a gastroesophageal pressure difference of approximately 11 cmH_2O is measured during voluntary relaxation against an obstructed airway above

20% VC (120). This is subtracted from all measurements of gastroesophageal pressure differences to obtain Pdi. In the lateral posture, gastroesophageal pressure differences during voluntary relaxation against an obstructed airway at high lung volumes were only 0, 2, 0, and 3 cmH_2O in the four subjects, respectively. We, therefore, assumed that the recorded pressure difference did in fact reflect Pdi at all lung volumes provided that the gastric balloon remained at the same horizontal plane. Complete relaxation of the diaphragm was never achieved at the onset of inspiration despite the voluntary attempts at diaphragmatic relaxation. Mean values of Pdi recorded at 20, 40, 60 and 80% VC with the diaphragm 'relaxed' were 8, 9, 10 and 15 cmH_2O, respectively.

All signals were recorded on a Hewlett-Packard strip-chart recorder, and Pdi and flow were both displayed on a large oscilloscope in front of the subject.

d) Results

1) Regional Lung Volumes: No systematic differences were apparent between any two counters at the same vertical level. Consequently, measurements of regional volume obtained from each pair of counters situated at a given vertical height, were averaged. A representative distribution of regional lung expansion at four different lung volumes is shown in Fig. 3. The upper panel represents the pattern of regional alveolar expansion when the diaphragm is 'relaxed' (low Pdi). The lower panel shows the distribution of regional

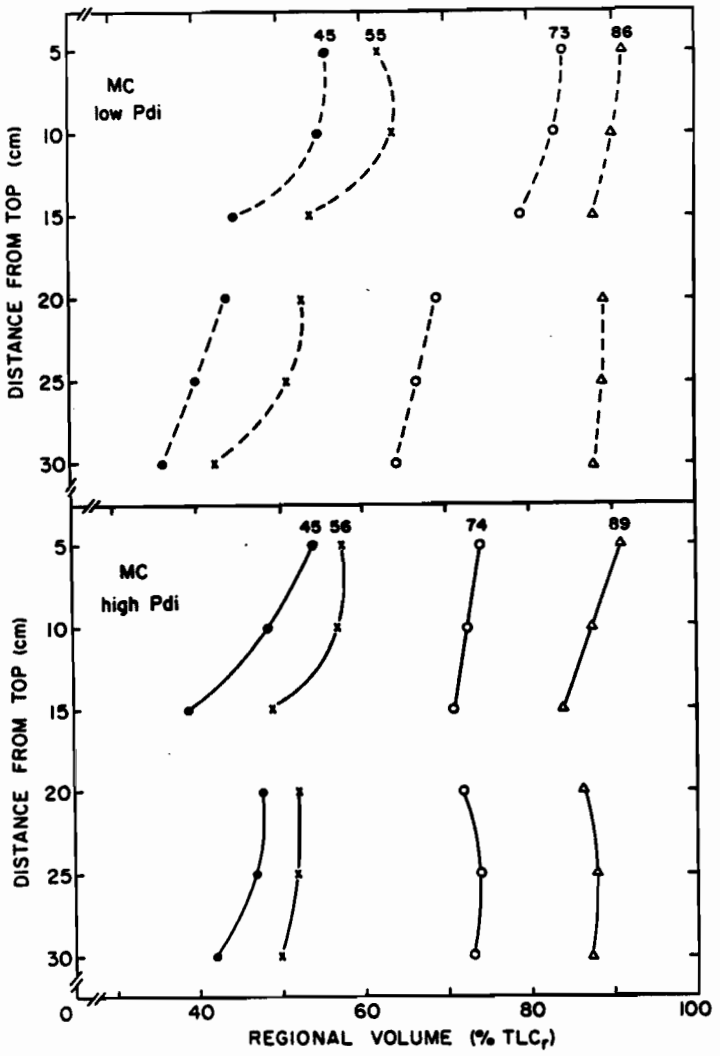

Figure 3: Vertical distribution of regional volume in one subject at four different lung volumes when diaphragm is 'relaxed' (upper panel) and when it is voluntarily contracted (lower panel). Numbers on top of each panel denote overall lung volume (%TLC) at which measurements were made. Note: 1) Gradient of alveolar expansion is greater when Pdi is lower (upper panel) than when Pdi is high (lower panel). 2) Gradients in regional volume are neither linear nor continuous in that they cannot be easily represented by single smooth curves.

volumes at the same four overall lung volumes when the diaphragm was voluntarily contracted (high Pdi). Except for the measurements at the high lung volume it is apparent that the vertical difference in alveolar expansion between the uppermost and lowermost two counterfields was greater when Pdi was low than when Pdi was high. Furthermore, the gradient in regional volume of the upper lung, represented by the upper 3 pairs of counters, and that of the lower lung, represented by the lower 3 pairs of counters are not linear and cannot be easily represented by a single smooth curve. This was observed in each subject. When Pdi was low the dependent lung as a whole appeared very much less expanded than the nondependent lung, especially in the midrange of lung volumes.

The relationship between regional lung volume, expressed as a fraction of regional TLC, and overall lung volume in each of the four subjects is shown in Figs. 4,5, 6 and 7, respectively. Panels A and C in each figure represent the uppermost and lowermost lung regions (5 cm and 30 cm from the top) under conditions of low Pdi and high Pdi, respectively. Panels B and D represent lung regions 10 cm and 25 cm from the top under conditions of low Pdi and high Pdi, respectively. In each subject measurements of regional volumes following passive inflation from a given overall lung volume did not differ from measurements made after active inspiration with predominantly intercostal and accessory muscles (low Pdi). The pooled results of all four subjects for the means of the upper 2 pairs of counters and

Figures 4-7: (Fig. 4,p.48; Fig.5,p.49; Fig. 6,p.50; Fig. 7,p.51) Relationship between regional lung volume expressed as % of regional TLC (TLC_r) and overall lung volume expressed as % of TLC. A and C: uppermost (solid dots) and lowermost (crosses) lung regions (5 cm and 30 cm from the top). B and D: lung regions 10 cm (solid dots) and 20 cm (crosses) from the top. A and B: alveolar expansion when Pdi is low. C and D: alveolar expansion when Pdi is high. Note substantially smaller gradient in alveolar expansion when Pdi is high than when Pdi is low. Open circles and open triangles in A and B denote measurements obtained after passive inflation.

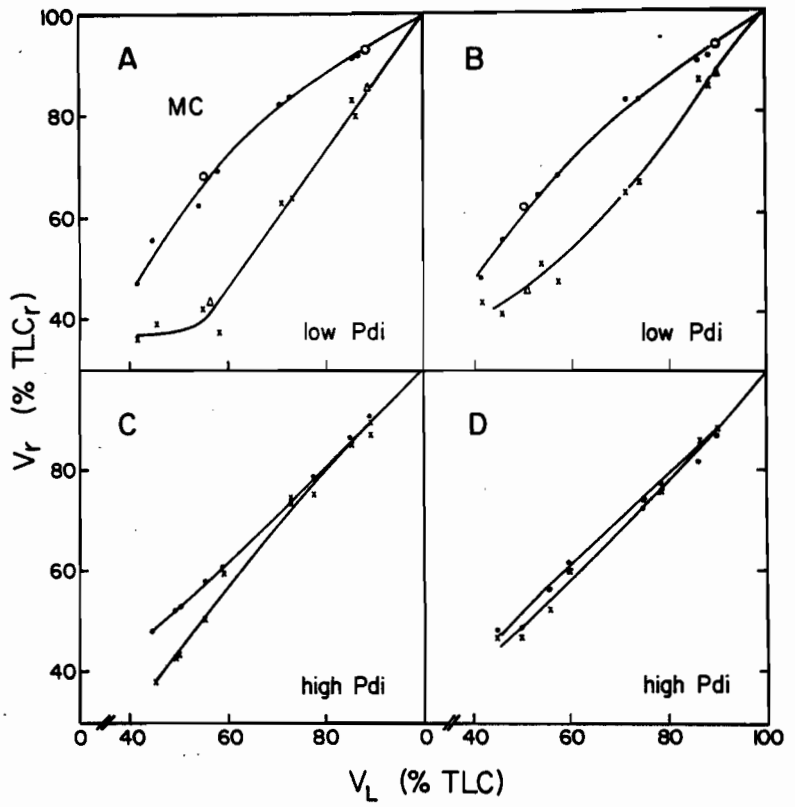
A
MC
low Pdi
B
low Pdi
C
high Pdi
D
high Pdi
100
80
60
40
0
40
60
80
100
Vr (% TLCr)
VL (% TLC)

Figure 4

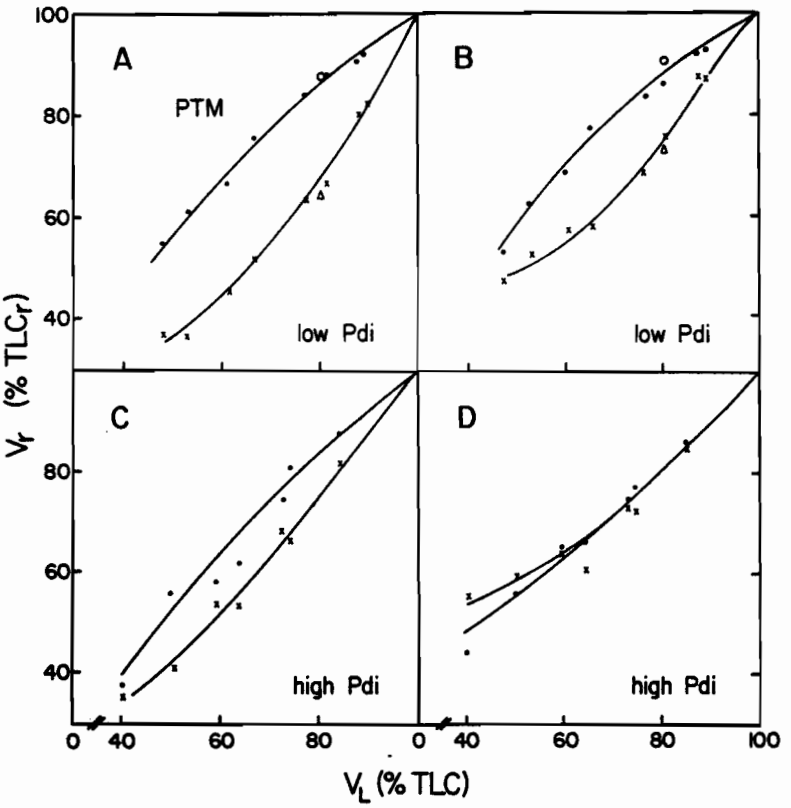
A
PTM
low Pdi
B
low Pdi
C
high Pdi
D
high Pdi
100
80
60
40
0
40
60
80
100
V_r (% TLC_r)
V_L (% TLC)

Figure 5

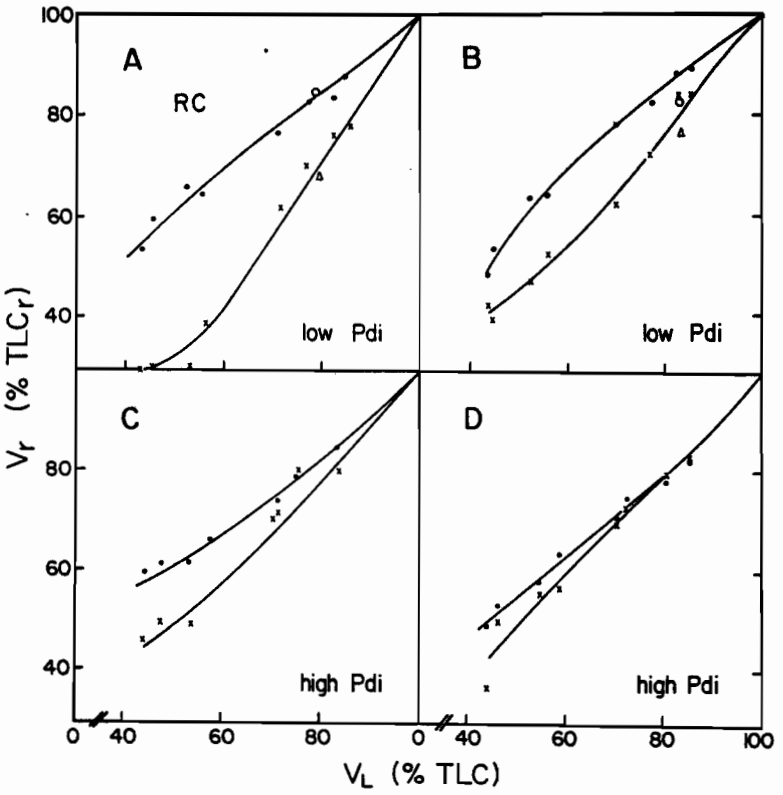
A
RC
low Pdi
B
low Pdi
C
high Pdi
D
high Pdi
100
80
60
40
0
40
60
80
100
V_r (% TLC_r)
V_L (% TLC)

Figure 6

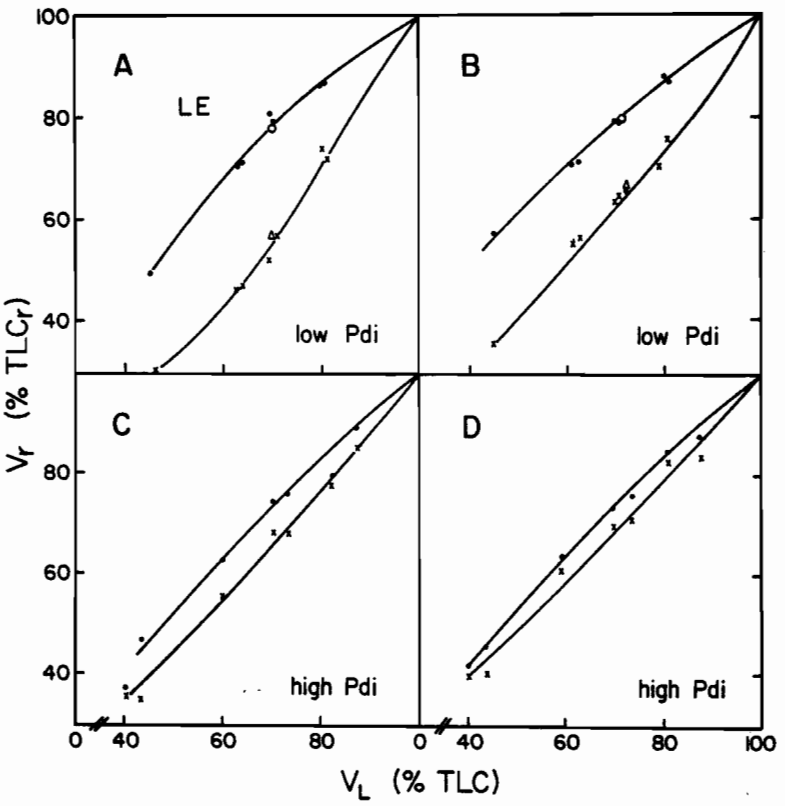
A
LE
low Pdi
B
low Pdi
C
high Pdi
D
high Pdi
100
80
60
40
0
40
60
80
100
V_r (% TLC_r)
V_L (% TLC)

Figure 7

the lower 2 pairs of counters are shown in Fig. 8. At all lung volumes the vertical gradient of alveolar expansion was greater when the diaphragm was 'relaxed' than when it was voluntarily contracted. At 70% TLC_r the vertical difference in alveolar expansion between the upper and the lower lung regions decreased from 19.7 ± 1.7 (mean ±1 SE) % TLC_r when Pdi was low, to 3.9 ± 1.5 % TLC_r when Pdi was high.

2) Expired Xenon 133 Concentration Versus Volume Curves: Because of an appropriate adjustment of the ^{133}Xe concentration inspired from the different lung volumes, the mean expired ^{133}Xe count rates were similar after each maneuver. Consequently, the expired alveolar plateaus were comparable. Figure 9 shows the results from one subject with the plateaus displaced for visual clarity. The slope of the expired plateau was steeper when inspiration of ^{133}Xe from each of the four lung volumes was performed with the diaphragm relaxed than under conditions when the diaphragm was voluntarily contracted. The difference was greatest at the midrange of lung volume (40 and 60% VC). Qualitatively similar results were obtained in each subject.

3) Helium Washout Curves:

a) Lateral position.

i) Relaxed expiration. The He washout during an RE maneuver showed the characteristic Phases I, II, and III. The FE_{He} rose abruptly at 58 ± 1.6% VC (means ± 1 SE) in all subjects and continued to rise as RV was approached

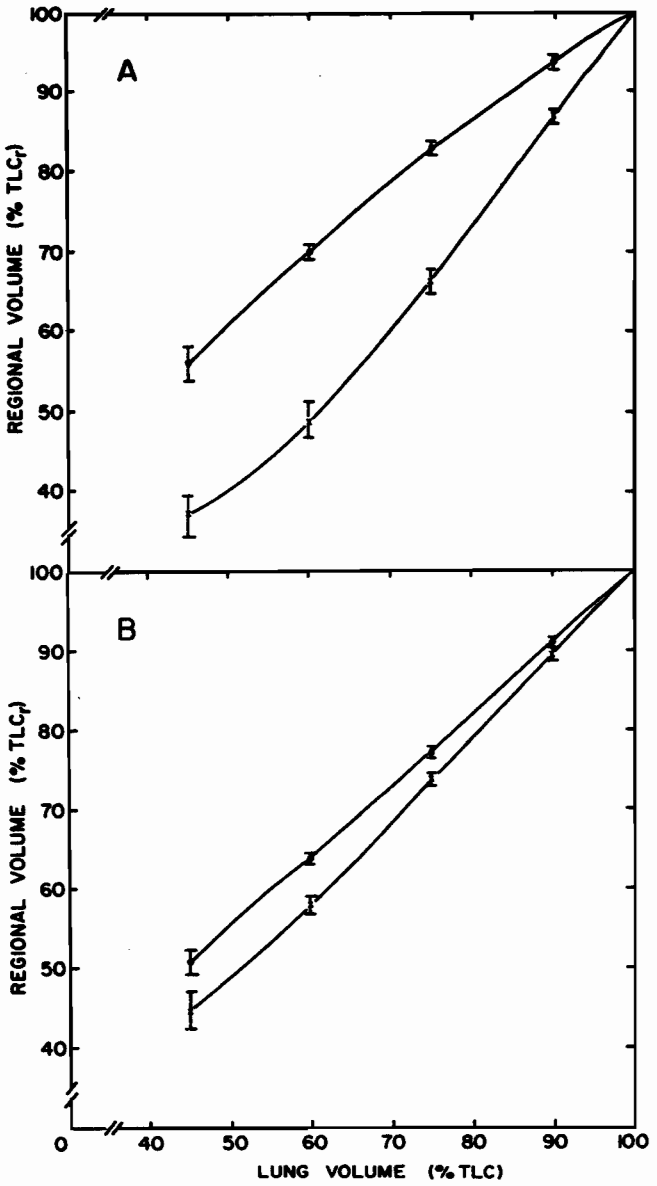

Figure 8: Regional lung volume plotted against overall lung volume. A: low Pdi; B: high Pdi. Bars indicate 1 SE on either side of mean. Axes as in Figs. 4-7. —●— Mean values of upper 2 pairs of counters. — x — Mean values of lower 2 pairs of counters. At all lung volumes vertical gradient of alveolar expansion was greater when Pdi was low than when Pdi was high.

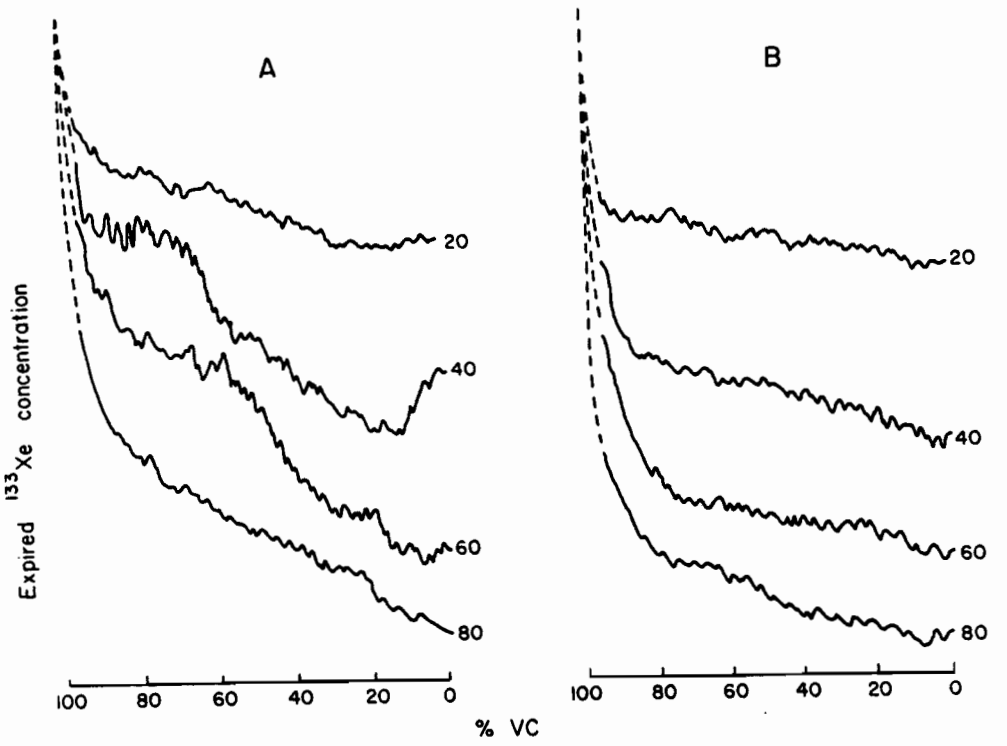

Figure 9: Expired ^{133}Xe concentration vs. volume curves following inspiration of ^{133}Xe to TLC starting from 20, 40, 60 and 80% VC, as indicated on right side of each panel. Plateaus have been separated for visual clarity. Ordinate is in arbitrary units. A: inspiration with low Pdi. B: inspiration with High Pdi. For each starting volume slope of expired curve is steeper after low Pdi inspiration than after high Pdi inspiration. See Results for further details.

(Fig. 10A). This portion of the expired tracing, which might be interpreted as a Phase IV, could be divided in some subjects into two separate segments, which were separated by a second inflection point at a volume corresponding to 10.6 ±1.0% VC.

During RE, the Pdi fell from approximately 40 cmH_2O at TLC to 5-10 cmH_2O at 80% VC. It remained at this value over most of the midlung volume range and rose gradually as RV was approached (Fig. 10A). The quasi-static pressure-volume (V-P) curve obtained during the He washout was similar to that of the erect subject.

ii) Expiration with voluntary diaphragmatic contraction. When the Pdi was maintained in excess of 30 cmH_2O, the pattern of He washout differed consistently from that seen during RE. The alveolar plateau had a constant slope down to 8.2 ±0.8 % VC, where an abrupt increase in $F_{E_{He}}$ constituted the onset of Phase IV (Fig. 10B). The $F_{E_{He}}$ on the alveolar plateau at lung volumes above 70% VC was approximately 1.3 ±0.05 (mean ±1 SE) times higher during VDCE than during RE (Fig. 11) but at lower volumes it was lower, with the result that the total amounts of He expired during VDCE and RE were the same. The quasi-static V-P curve was not systematically different from that obtained during RE. In every subject, the amplitude of the cardiogenic oscillations (ΔHe) was greater during VDCE than during RE. This difference was more marked at low lung volumes (Fig. 12).

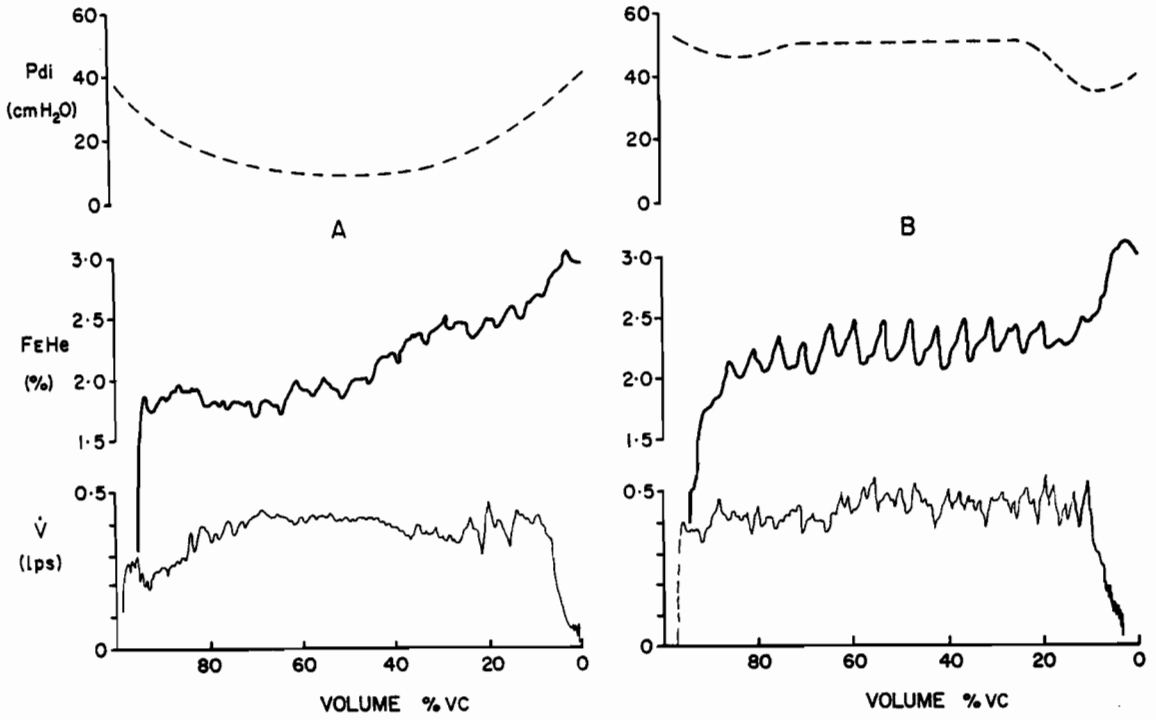

Figure 10: A: relaxed expiration (RE). B: expiration with voluntary diaphragmatic contraction (VDCE). Difference between RE and VDCE in pattern of the washout curves (middle panels) is related to different transdiaphragmatic pressure (upper panels), the expiratory flow rate during RE and VDCE (lower panels) having been similar.

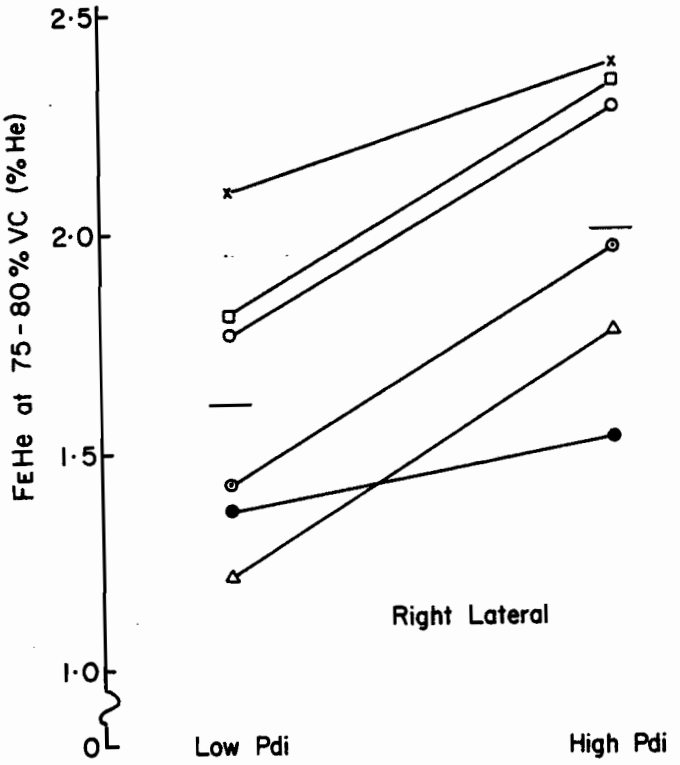

Figure 11: Expired He concentration ($F_{E_{He}}$) at 75-80% vital capacity (VC) was consistently higher during expiration with contracted diaphragm (high transdiaphragmatic pressure , Pdi) than it was during relaxed expiration (low Pdi). Different symbols represent different subjects. Bars are group means.

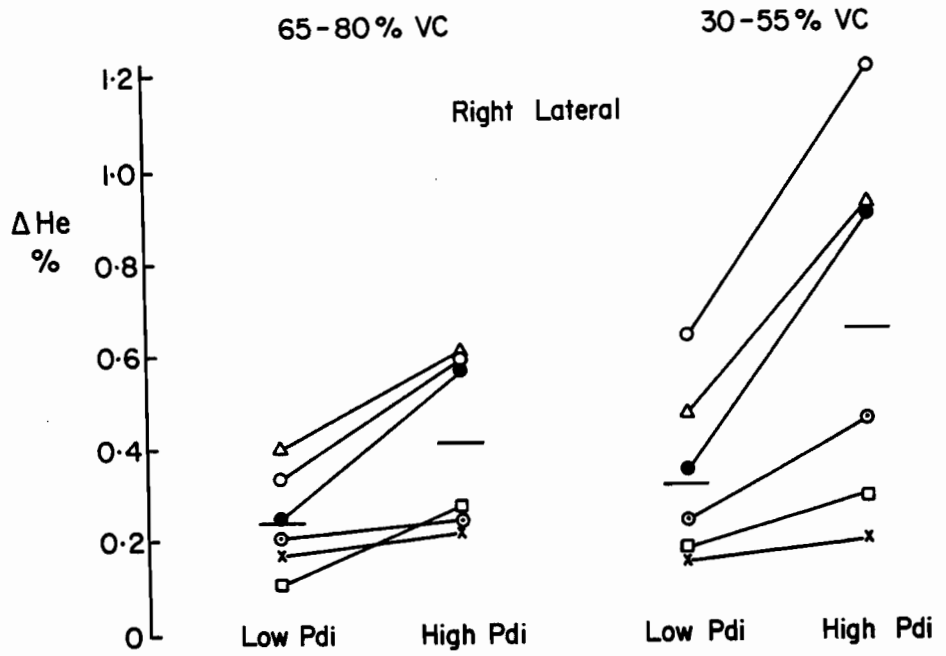

Figure 12: Amplitude of cardiogenic oscillations (Δ He%) during expiration with voluntary diaphragmatic contraction (high transdiaphragmatic pressure, Pdi) was consistently greater than it was during relaxed expiration (low Pdi), at both high and low lung volumes. Symbols as in Fig. 11.

In one subject in whom VDCE was performed at varying levels of Pdi, the slope of Phase IV progressively flattened as Pdi was increased up to 60 cmH_2O. Higher values of Pdi, maintained throughout expiration, did not change the washout.

iii) Expiration with step changes in Pdi. A step increase in Pdi during RE resulted in an abrupt and transient rise in $F_{E_{He}}$ (Fig. 13), but a step decrease during VDCE was followed by an abrupt and transient fall. Expiratory flow did not change. The $F_{E_{He}}$ after the rise or fall was not the same as it was before the changes in Pdi, and it differed at different lung volumes. Between 65 and 80% VC, following the transient rise, it was higher after a step increase in Pdi (Fig. 13), whereas between 20 and 55% VC, it dropped after the transient rise to a value smaller than that at the same volume during RE (Fig. 13). Step decreases in Pdi had the opposite effect on it at the respective lung volumes. Pooled data of the changes in $F_{E_{He}}$ (not including the transient deflections) produced by step changes in Pdi are shown in Fig. 14 for each of the two lung volume ranges.

In the three subjects who inhaled He boluses at different lung volumes, the slope of Phase IV became opposite to that seen after inhalation of a bolus at RV, even though the lung volume at which it was inspired was less than 50% VC. The tendency for Phase IV to flatten or reverse became greater in each subject as the lung volume at which the bolus was inspired became higher.

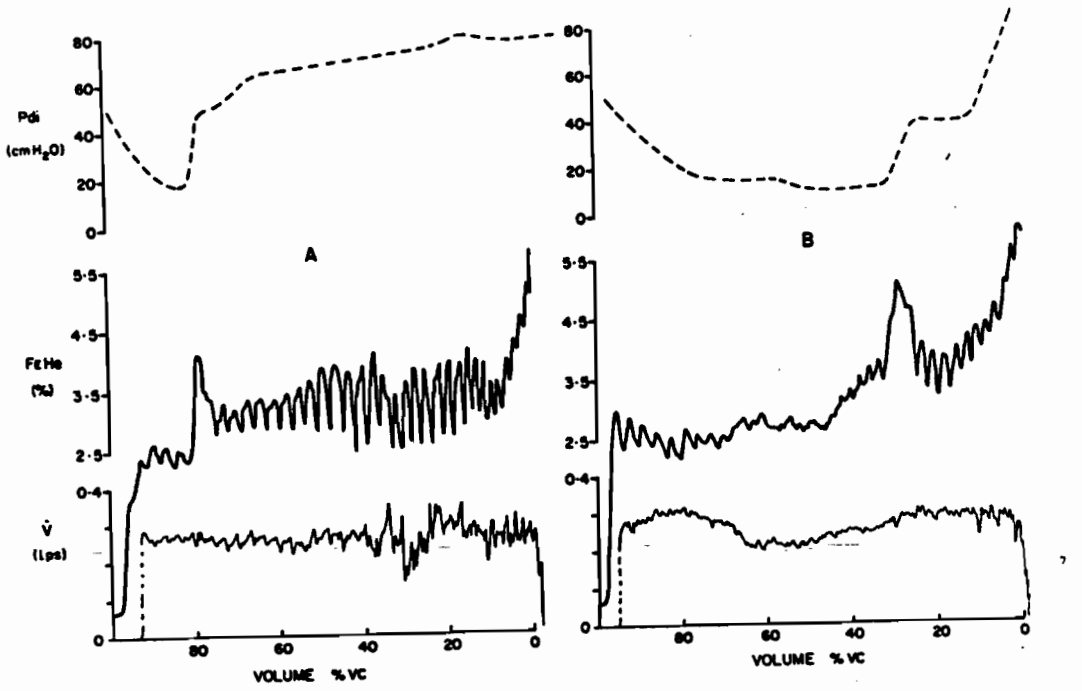

Figure 13: Effect of step increase in transdiaphragmatic pressure (Pdi) upon He washout. A: at high lung volume . B: at low lung volume. In both cases, the step increase in Pdi (upper panel) resulted in an abrupt and transient rise in expired He concentration (FE_{He}) (middle panel), which at high lung volume (A) was followed by a higher and at lower lung volume (B) by a lower FE_{He} than it was during a relaxed expiration (RE) maneuver. See text.

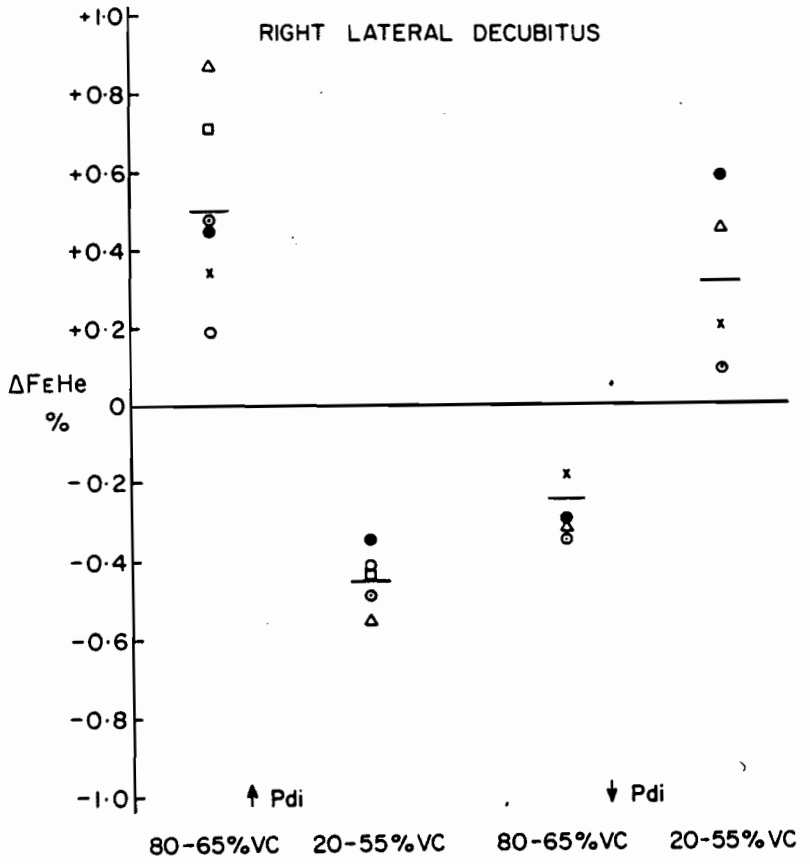

Figure 14: Changes in expired He concentration ($F_{E_{He}}$) following step increases (↑) or decreases (↓) in transdiaphragmatic pressure (Pdi) at two ranges of lung volume. Zero line: expired concentration without step change in Pdi. Symbols as in Fig. 11.

b) Supine position.

During RE the slope of the alveolar plateau remained constant at 0.36 ± 0.08 % He/ liter down to a closing volume of 15.4 ± 0.8 % VC. In contrast, during VDCE the slope of Phase III was 0.12 ± 0.05 % He/ liter ($P < 0.05$; Fig. 15) and closing volume decreased by 3.7 ± 0.4 % VC ($P < 0.05$; Fig. 16).

e) Discussion

The studies with ^{133}Xe indicate that in the lateral decubitus posture the vertical gradient of alveolar expansion is markedly influenced by the magnitude of diaphragmatic tone (Fig.16). Assuming that contraction of the diaphragm does not change the elastic properties of the lung, a reduced vertical gradient of regional expansion implies a reduced gradient of pleural pressure. When lung expansion is not isotropic, the calculation of pleural pressures from measurements of regional expansion may not be accurate. Nevertheless, a semi-quantitative assessment of the changes in pleural pressure gradient can be obtained by assuming a uniform distribution of elastic properties throughout the lung, and relating the changes in regional volume to the measured pressure volume curve in each subject. The calculated vertical pleural pressure difference at 70% TLC was divided by the distance between the respective counterfields and the result expressed as a pleural pressure gradient. Voluntary contraction of the diaphragm decreased the gradient from 0.23 ± 0.03 cmH_2O/cm to 0.04 ± 0.01 cmH_2O/cm, a factor of

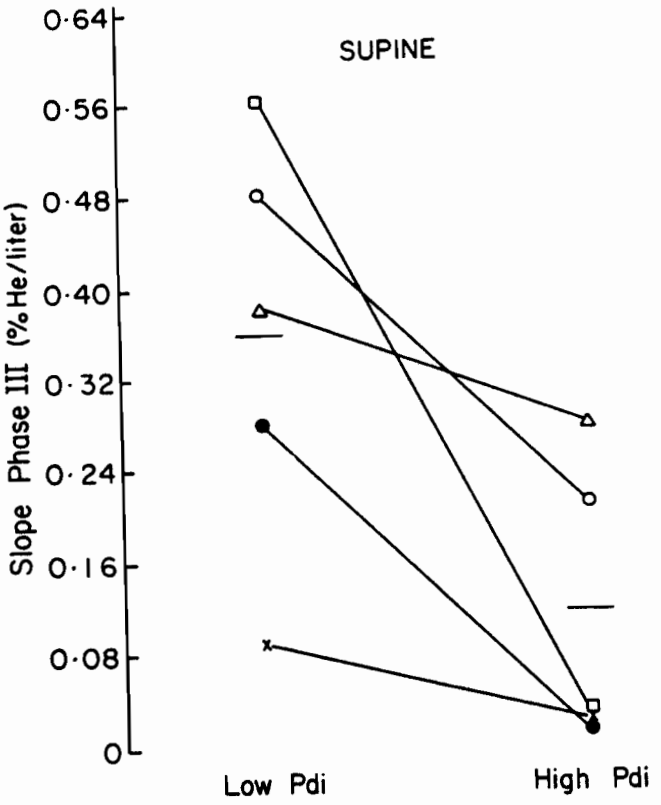

Figure 15: Effect of diaphragmatic tone on slope of Phase III in supine subject. During relaxed expiration (low transdiaphragmatic pressure (Pdi) slope of Phase III was higher than it was during expiration with contracted diaphragm (high Pdi). Symbols as in Fig. 11.

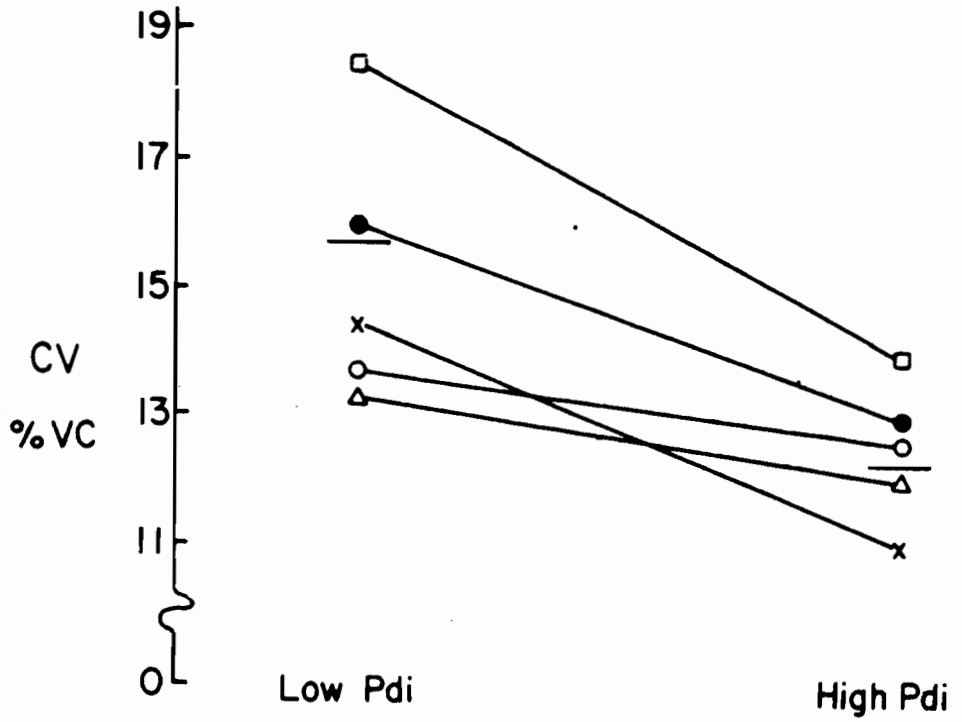

Figure 16: Effect of diaphragmatic tone on closing volume (CV) in supine subjects. CV was consistently lower during expiration with contracted diaphragm (high transdiaphragmatic pressure, Pdi) than it was during relaxed expiration (low Pdi). Symbols as in Fig. 11.

six.

In the horizontal subject, the factors determining dPpl/dD are 1) the weight of the lung (61), 2) the weight of abdominal contents (74), 3) the relationship between the shape of the rib cage and the shape of the lung (75,96), 4) the elastic properties of the lung (102), and 5) the effect of gravity on the chest wall shape (75). It is most unlikely that during VDCE either the elastic properties or the weight of the lung changes. However, the influence of the abdominal contents must differ. The diaphragm separates the abdomen and its contents from the thoracic cavity. When the subject is horizontal and relaxed, the diaphragm provides a highly compliant partition allowing the weight of the abdomen to act on the rib cage. Agostoni et al (75) demonstrated that dPpl/dD measured in horizontal animals decreased two-to-threefold after evisceration. In man, the diaphragm during contraction becomes rigid, effectively isolating the thoracic cavity from the influence of the abdomen. Thus with the diaphragm contracted, the influence of the abdominal contents on the dPpl/dD and hence on the regional lung volume and the pattern of lung emptying may be substantially reduced.

In addition, contraction of the diaphragm may have also a direct effect on the rib cage, tending to flare the caudal ribs outward. This would decrease the Ppl over the corresponding portions of the lung, as seen in horizontal animals during electrophrenic stimulation (110,111). If, due to gravity, the dependent part of the rib cage were less expanded when the subject is relaxed, then, during diaphragma-

tic contraction when the chest wall is more rigid, the change in pleural pressure caused by expansion of the rib cage would be greater over dependent lung regions. This would constitute a decrease in the dPpl/dD, as suggested in our studies.

Finally, it is conceivable that if the weight of the mediastinum contributes to the pleural pressure over the lower lung regions, then, during diaphragmatic contraction, tensing of the mediastinum may result in lower applied pressure over the mediastinal surface of the dependent lung. This would decrease dPpl/dD. Radiological observations support this possibility. The mediastinum is lifted up during each inspiration when the subject is in the lateral decubitus position (121), and during diaphragmatic contraction as performed in our study, the mediastinum was elevated in relation to its relaxed position (Fig. 1). The observation that cardiogenic oscillations increased during VDCE (Fig. 12) could be explained on the basis of greater tension of the mediastinum. Tight mediastinal tissues would facilitate the transmission of the cardiac impulse to the lungs.

In small anesthetized animals, the gradient in pleural surface pressure in the lateral decubitus posture is much greater than in the head-up position (78). We speculated that this might also be true in human subjects when the diaphragm was relaxed. Our results indicate however, that the calculated pleural pressure gradient was similar to that seen in the erect posture (56). Furthermore, if the weight of the abdominal contents results in a hydrostatic gradient of pressure (1 cmH_2O/cm) which is

applied to the diaphragmatic surface, why does the lung not reflect this gradient? There are several possible explanations: First, our measurements indicate that the 'relaxed' diaphragm may in fact be under tension. This could be due to persistent tonic reflex muscle activity and/or a passive stretching of the diaphragm particularly in the dependent diaphragmatic regions, which might be more stretched than the nondependent. Consistent with the former is the observation that in anesthetized, paralyzed subjects in the lateral decubitus posture the dependent diaphragm is displaced cephalad relative to its position in the awake state (114). In either case, in the presence of tension, the smaller radius of curvature of the dependent hemidiaphragm could result in the development of a greater pressure opposing the hydrostatic pressure in the abdomen. A tense diaphragm could thus impede the transmission of the abdominal pressure gradient to the thoracic cavity. It should be noted that to the degree that the weight of the mediastinum contributes to the gradient of alveolar expansion, not all of the calculated pleural pressure gradient is due to the transmission of the abdominal pressure gradient to the thorax.

Our measurements of the vertical distribution of regional volumes with 'relaxed' diaphragm differ from those of several previous studies. In contrast to Kaneko et al (57), we did not represent the relationship between regional volume and vertical distance from the top of the lung by a linear regression, but joined the data points with a smooth curve.

We felt this representation was more realistic and allowed us to make several interesting observations. From Fig. 3 it is apparent that the vertical gradient of expansion is interrupted at the level of the mediastinum so that the two lungs have qualitatively similar but discontinuous distributions of regional volume. At mid-lung volumes, this discontinuity is particularly marked. In both lungs the middle region is the most expanded. The reason for this is not entirely clear. The weight of the mediastinum could account for the relative deflation of the uppermost region of the dependent lung, but a similar pattern in the nondependent lung cannot be easily explained in this way. The behavior of the lungs as two relatively independent units is further illustrated by their response to diaphragmatic contraction (Fig. 3). The vertical gradient of expansion in the dependent lung was abolished or even reversed, whereas the gradient in the upper lung was diminished to a smaller degree. The volume redistribution between the two lungs must have been substantial.

When the diaphragm is 'relaxed' the relationship between regional volume and overall lung volume is alinear (Fig. 7A) indicating that the relative volume changes of different lung regions are not constant, even above FRC. This is in agreement with the measurements of Rehder et al (122) in anesthetized and paralyzed normal subjects, but differs from the conclusions of Kaneko et al (57). The ratio of the slopes of the two curves in Fig. 8 has been plotted against overall lung volume (Fig. 17). The plot reflects

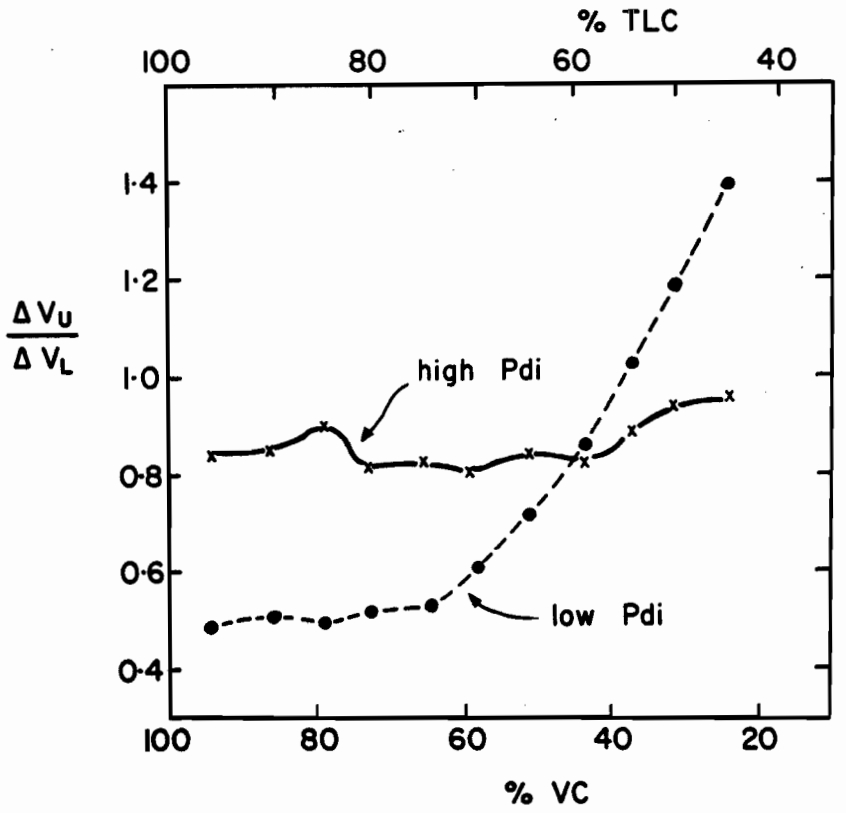

Figure 17: Relative volume changes of upper and lower lung regions plotted against overall lung volumes. Ordinate is equivalent to ratio of slopes of two pairs of curves in Fig. 8 calculated at intervals of 5% TLC. With low Pdi, ratio increases abruptly at approximately 60% VC, indicating relatively smaller volume changes of dependent lung regions. With high Pdi, relative changes in regional volumes are constant over most of VC.

the relative rates of change of upper and lower lung regions at different lung volumes. A surprisingly abrupt change in the ratio is seen at approximately 60% VC. At lower lung volumes the ratio progressively increases, indicating progressively smaller relative changes in volume of dependent lung regions. This plot bears a remarkable similarity to tracings of expired He concentration plotted against expired volume, after inhalation of a bolus of He at RV (Fig. 10A).

When the diaphragm is voluntarily contracted, the relative changes in regional volumes are constant over most of the volume range, as indicated by a relatively constant ratio of the two slopes (Fig. 17). Again, the ratio plot bears a close similarity to He bolus washouts performed with a contracted diaphragm (Fig. 10B). Thus, the expired He versus volume tracings can be accounted for by the vertical sequence of emptying of topographically distributed lung regions both when the diaphragm is relaxed and when it is voluntarily contracted.

In analyzing the He data, we assumed that any stratified inhomogeneity present in the lungs would be uninfluenced by the state of diaphragmatic contraction. Since the amount of He inhaled at RV as well as the inspiratory flow were identical in the maneuvers, we assumed that the vertical He concentration gradient at the beginning of expiration was always the same. Therefore any differences in the He washout between RE amd VDCE must have been due to differences in lung emptying.

Inhalation of a bolus of ^{133}Xe at RV by subjects in the lateral position produces very much greater ^{133}Xe

concentrations at the top of the lung than at the bottom (82). Correlation of regional ^{133}Xe concentration with expired ^{133}Xe washouts indicates that the lowermost lung regions tend to empty first, whereas the uppermost contribute more at lower lung volumes. Furthermore, this pattern of sequential emptying is gravity-dependent (82). Similar conclusions are deduced from Fig. 9. In the present study, the increase in the slope of the $F_{E_{He}}$ at 58% VC during RE indicates a progressive increase in the contributions from the He-rich uppermost lung regions. This observation is similar to that of other investigators (82, 123). However, during VDCE the pattern of lung emptying was radically different. The higher $F_{E_{He}}$ during the first portion of the expiration indicates that the fractional contribution from the He-rich upper lung regions was greater, but the decreased $F_{E_{He}}$ during the latter part of the expiration suggested an increased contribution from the lowermost zones. This signified a considerable decrease in the degree of sequential emptying, the different lung regions contributing more uniformly to the expirate. Similar conclusions can be drawn from the ^{133}Xe washout curves of Fig. 9, which show that the distribution of inspired ^{133}Xe, or of regional volume, was more homogeneous at all lung volumes when the diaphragm was contracted than when it was relaxed.

The changes in $F_{E_{He}}$ following step changes in transdiaphragmatic pressure (Pdi) confirmed the influence of diaphragmatic contraction on the pattern of lung emptying (Fig. 6). An understanding of the topographical basis for

these changes may be gained from a two-compartment model analysis in which regional volume of each compartment is plotted against overall lung volume (56,57). Because of the gradient in pleural pressure, the upper region is always more expanded than the lower one (Fig. 18). If Pdi is increased over a small volume interval EF, during RE, then at a high lung volume, the distribution of regional volumes changes from a and b to c and d. During this change, all of the expirate will come from the upper region, resulting in a transient large increase in $F_{E_{He}}$ (Fig. 13). Subsequently, at lung volumes smaller than F, the $F_{E_{He}}$ will be greater than it was in the early part of the expiration because of the greater contribution of the total expirate from the He— rich upper compartment.

A step increase in Pdi (Fig. 18) at a low lung volume, E' (below 58%, VC), will also produce a transient increase in $F_{E_{He}}$, due to the redistribution of regional volume (a' and b' to c' and d'). However, following this transient, the $F_{E_{He}}$ will be less than it was during RE at the same lung volume. This is because the He-poor dependent regions now contribute more to the expirate (dashed lines in Fig. 18). Similarly, step decreases in Pdi during VDCE will be associated with changes in regional volume and in regional emptying opposite in direction to those discussed above.

The distribution of regional volume from a and b to c and d, as well as from a' and b' to c' and d' when Pdi is increased constitutes a decrease in the vertical

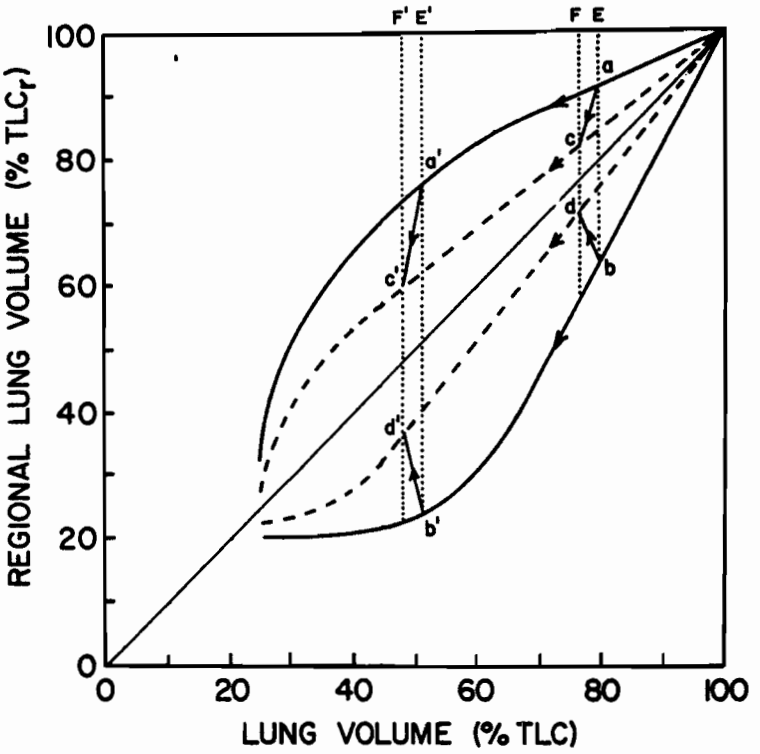

Figure 18: Two-compartment model representation of upper and lower lung regional volumes relative to overall lung volume (after Milic-Emili et al, 56). Solid lines: regional volumes during relaxed expiration. Broken lines: regional volumes during expiration with contracted diaphragm. Diagonal solid thin line: line of identity. Arrows between solid and broken lines show the change of regional volume during step increase in transdiaphragmatic pressure. See Discussion for further details.

gradient of alveolar expansion, as is shown with our ^{133}Xe studies (Fig. 8) , and it is consistent with the changes in the topographical distribution of alveolar distention observed at FRC in our preliminary radiological study (Fig. 1).

During VDCE in the supine subject, the slope of Phase III was consistently less and the closing volume was smaller than it was during RE (Figs. 15 & 16). These results are also consistent with the hypothesis that diaphragmatic tone influences the pattern of lung emptying in the supine posture in a manner similar to that in the lateral position.

The conclusion that voluntary diaphragmatic contraction changes the pattern of ventilation distribution, and hence dPpl/dD, raises the possibility that during spontaneous tidal breathing in the horizontal subject, dPpl/dD during inspiration, when the diaphragm is actively contracted, may differ from that during expiration, when the diaphragm is relaxed. There is considerable experimental as well as theoretical evidence to support this hypothesis. In the one subject in whom He washouts were performed during VDCE with Pdi maintained at different constant values, the pattern of lung emptying differed from that during RE, even when Pdi was held at 20 cmH_2O. This indicates that even mild degrees of diaphragmatic contraction influence ventilation distribution in the lateral decubitus position. Direct measurements in spontaneously breathing supine dogs by Farhi et al (115) showed that the swings of pleural pressure were greater in the diaphragmatic sinus at the posterior vertebral gutter than they were at other sites over the

costal surface of the lung. Similar measurements have not been made in man. However, Pdi rises during each inspiration and falls during expiration, reflecting the degree of contraction of the diaphragm. If during expiration the relaxed diaphragm allows greater deflation of dependent lung regions because of greater transmission of the hydrostatic pressure gradient of the abdomen, then upon inspiration, when the diaphragm is contracting, the influence of the abdomen on the lung will be diminished. Consequently, dependent zones will be exposed to a greater change in pleural pressure than nondependent regions and ventilation will be preferentially distributed to dependent zones to a greater extent than that predicted by the regional pulmonary compliance.

The reversal of Phase IV seen when the bolus was inhaled at a lung volume less than 50% VC would not have been consistent with airways closing at higher lung volumes in erect subjects (45). However, if as we believe, dPpl/dD decreases during inspiration and increases upon expiration, then theoretically the possibility that airways close at 58% VC cannot be excluded from these observations. During inspiration, the pleural pressure over the dependent lung regions may decrease markedly, exceeding the critical opening pressures, with consequent inflation of the lung. Thus, due to a greater swing in pleural pressure, the lower lung zones may be the first to inflate and the first to deflate. This explanation would be consistent with the fact that the dependent lung is better ventilated and contributes more to overall gas exchange (56, 124, 125, 126) even if the

closing volume exceeds FRC (127). However, a marked increase of closing volume in the lateral decubitus position seems unlikely. The volume of the dependent lung at FRC is the same as that in the supine subject (124, 128) despite the change in overall FRC. Since supine closing volume is similar to that in seated subjects (129), it is difficult to explain a marked increase in the lateral decubitus posture. Furthermore we did not observe any inflection point on the V-P curve at high lung volume which is suggested to be an indication of airway closure (85, 130). Finally our results with ^{133}Xe suggest that massive closure of airways in the dependent regions does not occur at high lung volume (58% VC) even when the diaphragm is 'relaxed'. Were this the case, then the lowermost lung region would not change its volume measurably between 50% and 20% VC. (Figs. 4-7). Yet only in subject MC (Fig. 4) was there a tendency for the volume of the lowermost region to remain constant between 40% and 20% VC. Our conclusion is consistent with the demonstration that in the lateral posture, N_2 closing volumes measured independently in each lung are not greater than in the erect position (131).

II. 2. 2) Voluntary Factors Influencing the Distribution of Inspired Gas.

a) Summary

This study was designed to assess the influence of voluntary patterns of respiratory muscle contraction on the distribution of inspired gas at low flows (0.4 liter per sec). Three types of inspiration were studied in 9 normal subjects in upright, supine, and lateral decubitus posture: (1) natural, (2) intercostal, during which rib cage expansion was accentuated by preferential use of intercostal and accessory muscles, and (3) abdominal, during which abdominal motion was enhanced. The types of inspiration were assessed by monitoring transdiaphragmatic pressure and the anteroposterior diameter of the rib cage and abdomen. Distribution of inhaled gas was measured directly in 4 seated subjects using Xenon 133 as tracer gas, and indirectly, by inference from helium bolus washouts in 5 subjects in upright, supine, and lateral postures. In all postures, the tracer gas inhaled at functional residual capacity could be distributed preferentially to dependent lung regions by an abdominal inspiration, whereas an intercostal inspiration resulted in a more even distribution, or one preferentially to the nondependent zones. When the tracer gas was inhaled at residual volume, differences in distribution between abdominal and intercostal inspirations were detected only in the lateral posture. Thus, in normal subjects distribution of inspired gas may be altered by voluntary use of different muscle groups. This implies

unequal regional pleural pressure swings that differ in the various breathing maneuvers.

b) Introduction

There is little evidence that the various breathing patterns alter the distribution of inspired gas. In fact, several studies have shown that topographic distribution of ventilation is unaltered, both in normal subjects and in patients with obstructive lung disease when different breathing patterns are used (107,116, 117,118).

In the previous experiment, it was shown that in the horizontal posture, the tension of the diaphragm substantially influences the vertical gradient of alveolar expansion and the pattern of lung emptying. Furthermore, both in upright and horizontal postures, different sequences of thoraco-abdominal motion measurably alter the pattern of lung emptying (132,133). These results suggested to us that intrapulmonary distribution of inspired gas may be sensitive to alterations of lung shape (134). We therefore systematically studied the distribution of inspired gas in different body positions after inspirations initiated by different muscle groups. Our results clearly show that specific voluntary patterns of respiratory muscle contraction substantially change the regional distribution of inspired gas in all postures. Furthermore, this voluntary influence is most marked and is easily achieved in the horizontal position, where its potential application to patients with lung disease may be most valuable.

c) Methods

We studied 8 normal men and 1 normal woman 30 to 45 years of age. Subjects were studied upright, supine , and in the right decubitus posture; however, not all of the subjects were studied in each of the 3 positions. Distribution of inspired gas in the lung was determined directly , using Xenon 133 (^{133}Xe) as the tracer gas, or ,indirectly, by inference from single-breath washouts of helium (He) (see following).

1) Type of Inspiration: The tracer gas was inspired in each of 3 different ways in each posture, and at least 2 runs were performed for each maneuver.

i) Natural inspiration. The subject inspired a predetermined volume of tracer gas at a constant flow of less than 0.5 liter per sec, continuing the inspiration to total lung capacity (TLC). He inspired naturally, inasmuch as he made no voluntary effort to influence the shape of the chest wall or the pattern of respiratory muscle contraction. Each inspiration was preceded by a constant-volume history consisting of an inspiration to TLC followed by 3 tidal breaths (Fig. 1).

ii) Intercostal inspiration. After a similar volume history, the subject inspired the tracer gas at a constant flow (< 0.5 liter per sec) using predominantly the intercostal and accessory muscles of the rib cage. In particular, he attempted to relax his diaphragm and abdominal muscles so that the abdomen was drawn inward during the

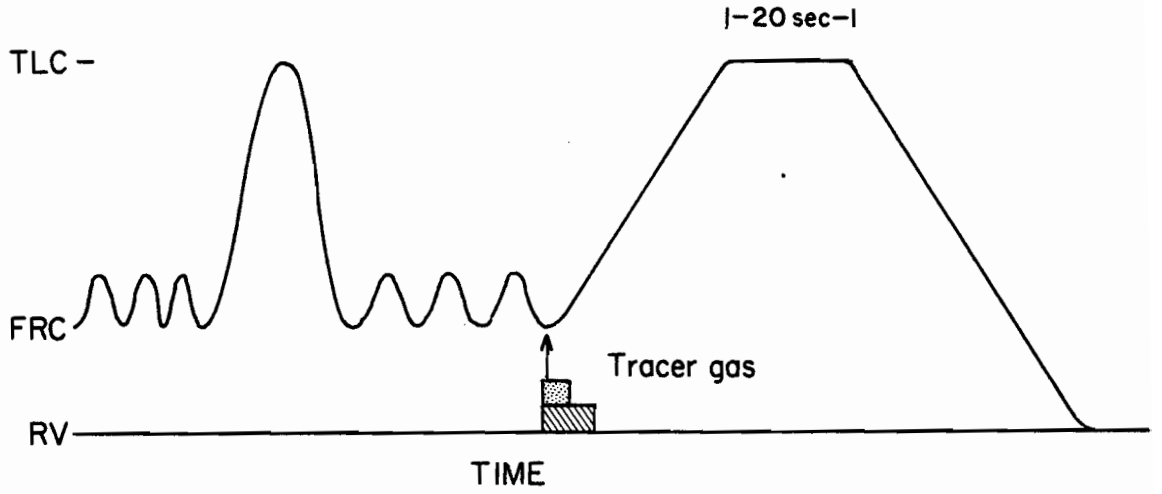

Figure 1: Experimental procedure during each maneuver. At the beginning of the slow inspiration either a bolus (4 ml of Xenon 133 (^{133}Xe) - arrow; 150 ml of helium (He, stippled area) or a tidal volume of tracer gas (500 to 600 ml of ^{133}Xe or He , dashed area) was inhaled. See Methods for further details. TLC = total lung capacity, FRC = functional residual capacity, RV = residual volume.

initial part of the inspiration (Fig. 2). The subjects were aided by an oscilloscopic display of the anteroposterior diameters of the rib cage and abdomen on an X-Y plot (135,136) as well as by a visual display of transdiaphragmatic pressure (Pdi), which had to remain unchanged during the first 600 ml of the inspiration. If Pdi increased significantly, the run was discarded. We interpreted an unchanging Pdi as signifying a 'relaxed' diaphragm so that pleural and abdominal pressures decreased by equivalent amounts, and the diaphragm was drawn upward. After a volume greater than 600 ml had been inspired, the subject continued to TLC using all respiratory muscles.

iii) Abdominal inspiration. After a similar volume history, the subject inspired the tracer gas at a constant flow (0.5 liter per sec) by contracting his diaphragm and pushing out the abdominal wall. This was associated with a large increase in Pdi and in the anteroposterior diameter of the abdomen, whereas the anteroposterior diameter of the rib cage remained unchanged, or decreased, during the first part of the inspiration (Fig. 2). When these changes in anteroposterior diameters were not observed, the run was discarded, because an increase in Pdi can be obtained without significant abdominal motion by simultaneous contraction of the diaphragm and abdominal muscles. After at least 600 ml had been inspired, the subject continued to TLC using all inspiratory muscles.

Similar types of inspiration were performed when the tracer gas was inhaled from residual volume (RV). How-

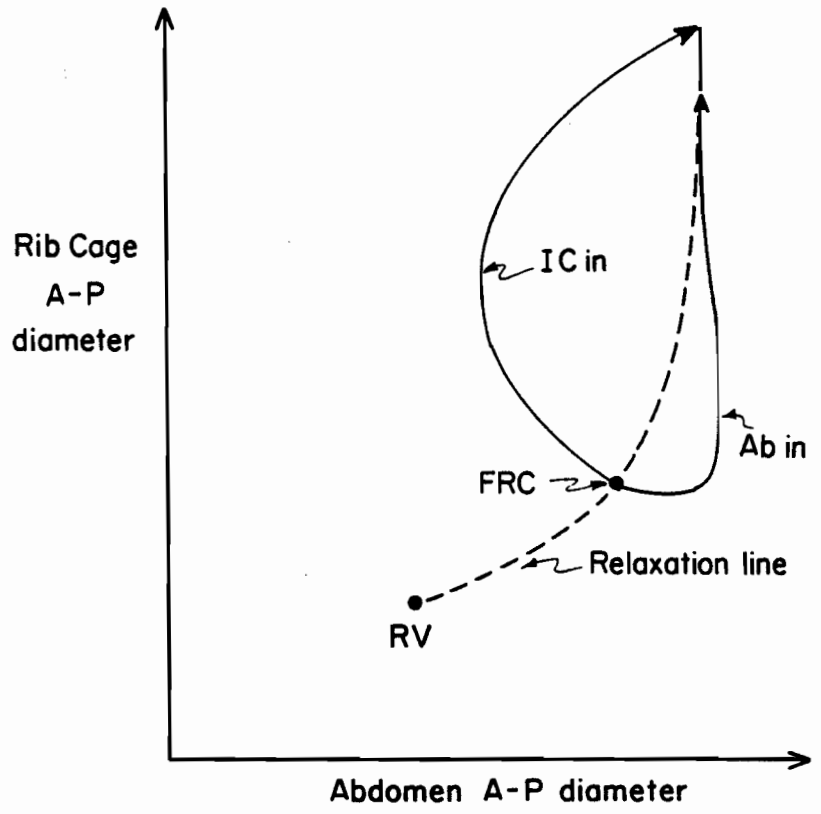

Figure 2: Diagrammatic representation of thoracoabdominal shape (136), during relaxation against obstructed airway (dashed line), during inspiration initiated mainly with intercostal and accessory muscles (IC in), and during inspiration initiated with enhanced abdominal motion (Ab in). A -P = anteroposterior, FRC = functional residual capacity, RV = residual volume.

ever, in that position we only monitored rib cage and abdominal anteroposterior diameters whose changes were similar to those obtained at functional residual capacity (FRC). The Pdi was not monitored because the esophageal pressure near RV may not accurately represent pleural pressure.

2) Type of Expiration: When distribution of inspired gas was measured indirectly, by inference from expired volume versus He concentration curves, the pattern of expiration was rigorously standardized. Expiratory flows were kept constant at <0.5 liter per sec with the aid of an expiratory resistance, and a fixed sequence of thoraco-abdominal motion was used. The subjects expired from TLC to mid-vital capacity (VC) by decreasing the anteroposterior diameter of the abdomen while actively maintaining rib cage expansion. Subsequently, both rib cage and abdominal anteroposterior diameters were allowed to diminish as expiration to RV was continued. Just as during inspiration, the subjects were aided by an oscilloscopic display of the anteroposterior diameters of the rib cage and abdomen on an X-Y plot (10). A standardized sequence of thoraco-abdominal motion increased the reproducibility of the expired gas concentrations and allowed for a better resolution of differences in distribution of the inspired He. We have previously shown that the pattern of lung emptying is influenced by the sequence of thoracoabdominal motion, and that the pattern described previously results in a more linear and steeper alveolar plateau both in the upright

posture (132) and in the horizontal posture (133). The Pdi remains low during most of the expiration, increasing as RV is approached, as in an ordinary normal slow expiration.

3) Studies Using ^{133}Xenon: Four male seated subjects inspired at FRC either a bolus of 4 ml of ^{133}Xe-labeled gas (~1 mCi) injected into the mouthpiece, or a 500 ml tidal volume (V_T) of ^{133}Xe-labelled gas (~2 mCi per liter), followed by air to TLC. Intercostal and abdominal inspirations were randomized and at least 2 runs were obtained with each type, both for bolus and V_T inspirations. For technical reasons, the distribution of ^{133}Xe labeled V_T breaths was not measured in one of the 4 subjects. At TLC, the subject held his breath with a closed glottis while the regional ^{133}Xe count rates were measured with 6 pairs of horizontal scintillation detectors positioned 5 cm apart vertically behind the chest. Skin markings made on the chest of each subject assured constancy of position during counting at TLC. An additional scintillation detector, positioned over the trachea, recorded the passage of ^{133}Xe-labelled gas through the trachea during inspiration. This allowed us to determine the volumetric dispersion of the tracer at the level of the trachea both when a bolus and when a V_T was inspired. Regional concentrations after each inspiration were calculated from the regional count rates by comparison with those obtained after equilibration with a known ^{133}Xe concentration (44). Regional concentrations were expressed

as percentages of those that would be measured after uniform distribution of the tracer gas (137). Data analysis was performed on-line by a Data General computer with off-line plotting of all regional count rates for data storage. Flow was measured by a pneumotachograph and a Validyne differential pressure transducer whose signal was integrated to measure volume. The Pdi and gastric pressure were obtained as is described in the methods of experiment II.2.1.

The anteroposterior diameters of the rib cage and abdomen were measured with 2 pairs of linearized magnetometers (135,136). One pair was positioned half-way between the angle of Louis and the xiphoid cartilage, and the other pair was just cephalad to the umbilicus. The magnetometers were calibrated during isovolume maneuvers (136) to produce equal signals for equivalent volume changes of the rib cage and abdomen. The signals were displayed on X and Y coordinates of an oscilloscope as well as on an 8-channel strip chart recorder. The latter also recorded gastric pressure, Pdi, flow, volume, and the count rates from the scintillation detector over the trachea.

4) Studies Using He: We recorded single-breath He washouts in the upright, supine, and lateral decubitus postures in 5 subjects inspiring the tracer gas from either FRC or RV.

i) Inspiration from FRC. After a volume history similar to that used during ^{133}Xe studies, each subject inhaled either 150 ml (bolus) or 600 ml (V_T) of 100 per cent He, followed by air to TLC. Natural, intercostal, and abdominal inspirations were randomized, but at least 2 of each were performed by each subject in each posture. During the subsequent standardized expiration (See previous description), He concentration ($F_{E_{He}}$) was measured at the mouth.

ii) Inspiration from RV. After exhaling to RV, each subject inhaled a 150 ml bolus of He followed by air to TLC. At least 2 runs were made with a natural, intercostal, or abdominal type of inspiration. During the subsequent VC, expiration $F_{E_{He}}$ was recorded at the lips in the same manner as after inspirations from FRC. During these studies particular attention was paid to ensure that each subject inhaled the He bolus from true RV. Only when the inspired and expired VC matched to within 100 ml ($\sim$2 per cent VC) were the maneuvers accepted as satisfactory.

Measurements of flow, volume, gastric pressure, Pdi, and anteroposterior diameters of the rib cage and abdomen were made in exactly the same way as described for the ^{133}Xe studies. The magnetometers were calibrated in the upright posture. In addition, $F_{E_{He}}$ was measured with a mass spectrometer (Perkin-Elmer) and was recorded, together with expiratory flow, on the 2 ordinates of an XYY' recorder against expired volume on the abscissa. We calculated the amount of He exhaled during each maneuver from the $F_{E_{He}}$ and volume signals using an electrical product integrator.

This served as a check to ensure a constant bolus size and to permit quantitative comparison of the slopes of the alveolar plateau.

d) Results

1) Distribution of ^{133}Xe-labelled Gas in Upright Posture: There were no systematic differences in the count rates between the 2 counters of each pair situated at a given vertical height. Consequently, measurements obtained from each pair of counters were averaged.

A representative distribution of regional ^{133}Xe concentration in one subject is shown in Fig. 3. After an intercostal inspiration of a bolus of ^{133}Xe, relatively more ^{133}Xe was distributed to the upper and midlung zones and less was distributed to the bases than after an abdominal inspiration. We quantified these differences by calculating the ratio of the mean ^{133}Xe concentration in the uppermost 2 pairs of counters to that of the lowermost 2 pairs of counters (U/L). After an intercostal inspiration U/L in every subject was substantially greater (mean ± 1 SE, 0.89 ± 0.12) than after an abdominal breath (0.60 ± 0.10, $P < 0.01$). Similarly, the U/L of a V_T of ^{133}Xe labeled gas was consistently greater after an intercostal inspiration than after an abdominal inspiration ($P < 0.05$) (Fig. 4). The difference in distribution between intercostal and abdominal breaths, however, was smaller when a V_T was inspired than when a bolus was inhaled.

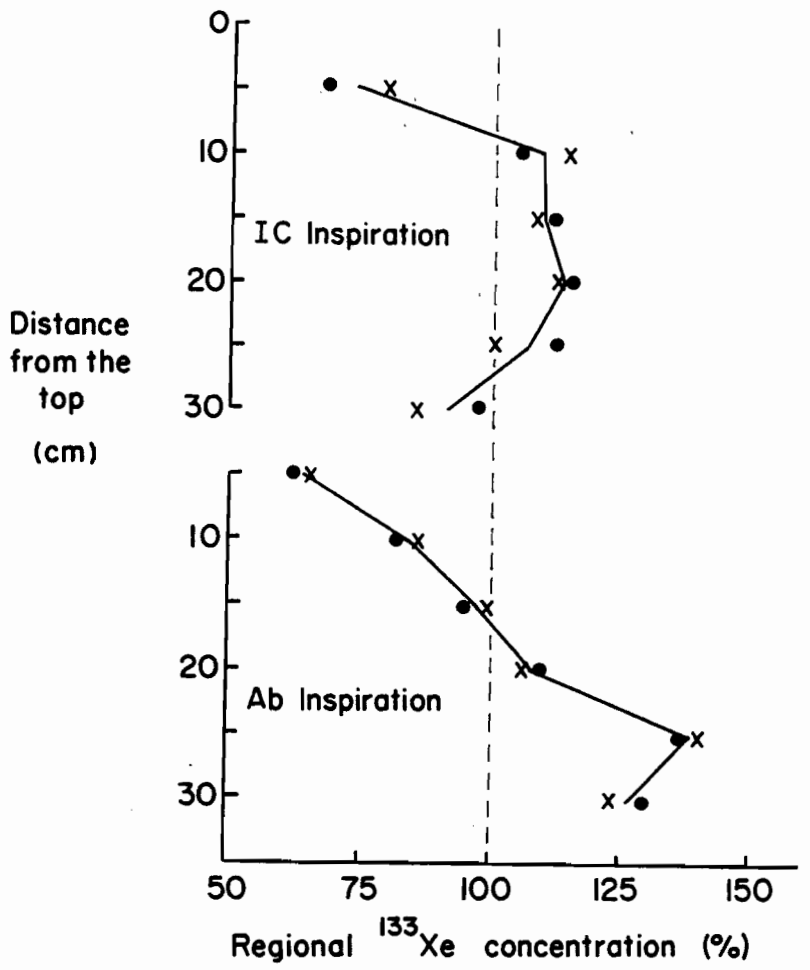

Figure 3: Regional distribution of a bolus of Xenon 133 (^{133}Xe) inhaled at 0.4 liter per sec from functional residual capacity in 1 seated subject. Upper panel. Inspiration using predominantly intercostal and accessory muscles (IC). Lower panel. Inspiration with enhanced abdominal motion (Ab). Different symbols indicate duplicate measurements. Abscissa is normalized alveolar ^{133}Xe concentration. Note preferential distribution of ^{133}Xe to basal regions after abdominal inspiration and to upper mid-zones after intercostal inspiration.

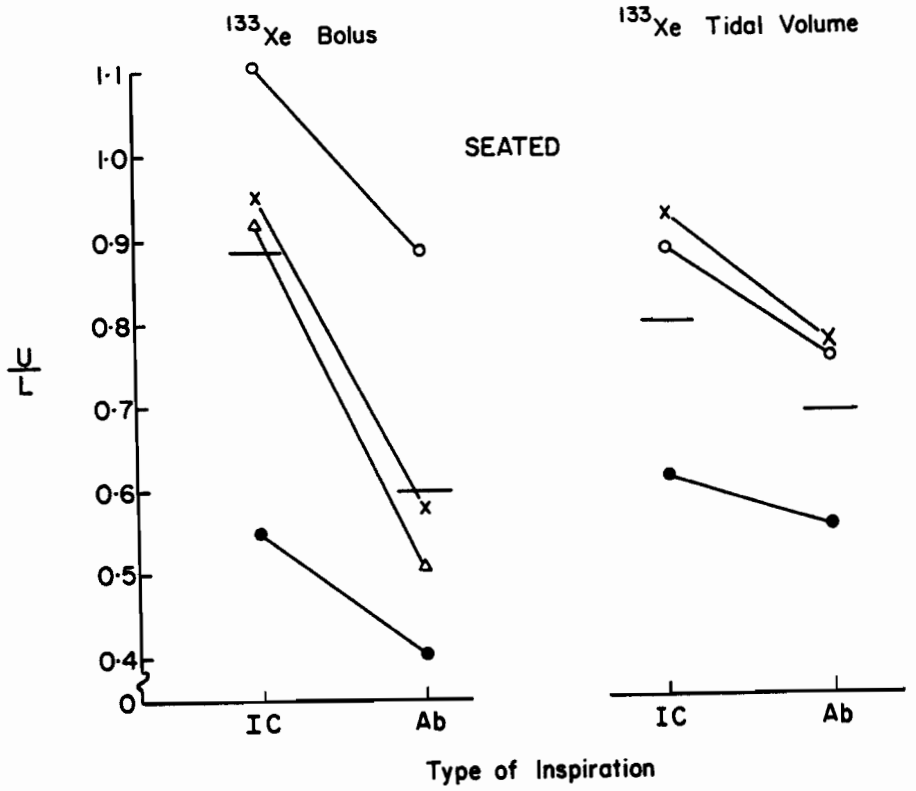

Figure 4: Relative distribution of Xenon 133 (^{133}Xe) between the 2 uppermost and the 2 lowermost counterfields (U/L ratio) in seated subjects. After an abdominal (Ab) inspiration, dependent lung regions received greater proportion of inspired tracer gas (4 ml left; 500 to 600 ml, right) than after an intercostal (IC) inspiration. Different symbols represent different subjects. Horizontal bars are mean values. Flows were <0.4 liter per sec.

2) Studies Using He-labelled Gas:

i) Inspiration from FRC. A representative example of a tracing obtained during expiration is shown in Fig. 5. This is a washout obtained in the right lateral decubitus posture after inhalation of 600 ml of tracer gas. The slope of the linear portion of the alveolar plateau after an intercostal inspiration is positive, whereas that after an abdominal inspiration is negative. In fact, in each of the 3 postures, in every subject, the slope of Phase III of the He washout (expressed as per cent He per liter of expired volume) was greater after intercostal than after abdominal inspirations ($P < 0.05$). After a natural inspiration, the magnitude of the slope was intermediate between those of the other 2 maneuvers. Pooled results from 5 subjects in the upright posture are shown in Figure 6.

In the horizontal postures, the results were qualitatively similar to those in the seated position. In 5 subjects who inspired 600 ml of He in the supine posture, the slope of the alveolar plateau was 0.29 ± 0.02 per cent He per liter after intercostal inspiration, 0.05 ± 0.12 per cent He per liter after a natural inspiration, and -0.10 ± 0.14 per cent He per liter after an abdominal inspiration (Fig. 7). Considerably greater differences were observed in the same 5 subjects in the right lateral decubitus position (Figs. 5 and 8). The slopes after an intercostal, a natural, and an abdominal inspiration of 600 ml of He were, respectively, 0.32 ± 0.13, -0.65 ± 0.31, and -1.66 ± 0.21 per cent He per liter. Distribution of a smaller volume

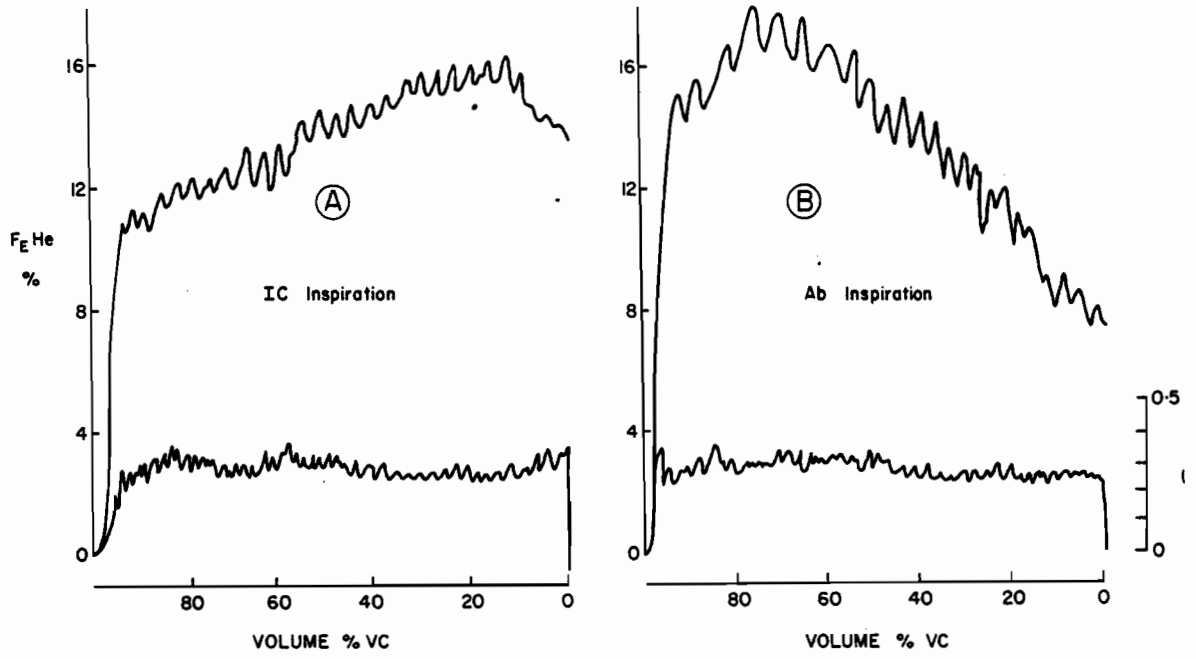

Figure 5: Expired helium concentration ($F_{E_{He}}$) vs. volume curves after inhalation of 600 ml of He from functional residual capacity in 1 subject in the lateral decubitus posture. Note differences in slopes of alveolar plateau at constant expiratory flows after inspiration. A. Using mainly intercostal (IC) and accessory muscles. B. With enhanced abdominal (Ab) motion. $\dot{V}$ = flow, in liter per sec.

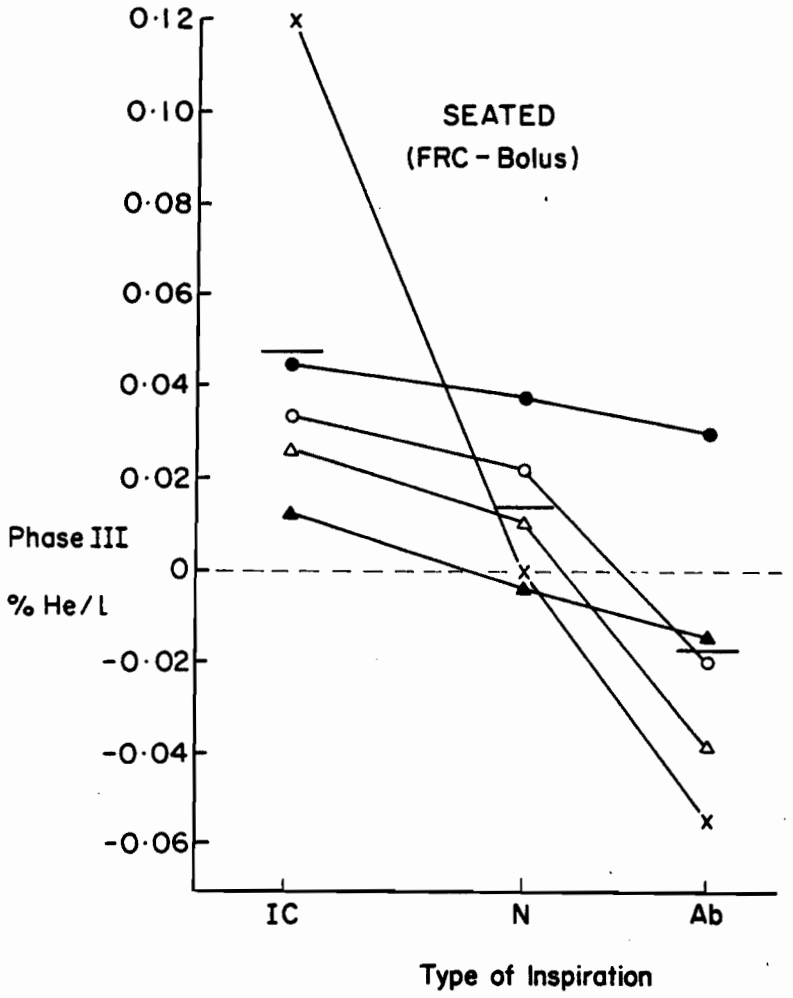

Figure 6: Effect of different patterns of inspiration on the slope of the helium (He) plateau in seated subjects; 150 ml of He were inhaled at 0.5 liter per sec from functional residual capacity (FRC). Different symbols represent different subjects. Horizontal bars are mean values. Slopes were most positive after intercostal (IC) inspiration, most negative after abdominal (Ab) inspiration, and intermediate after normal (N) inspiration.

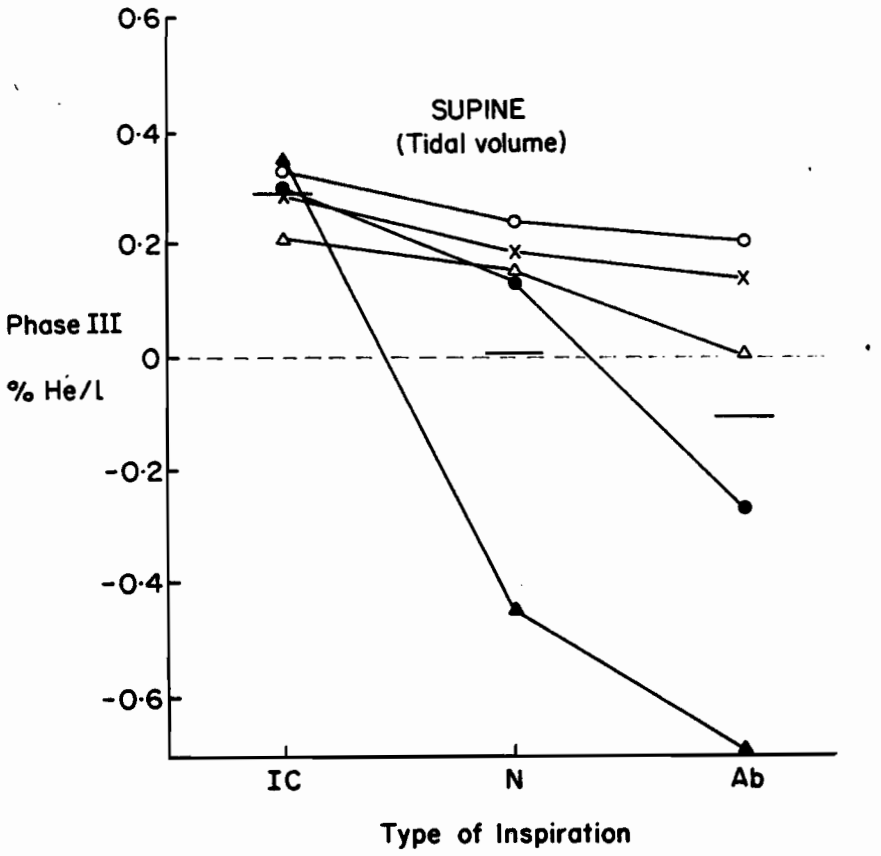

Figure 7: Influence of pattern of inspiration on slope of helium (He) plateau in supine subjects; 600 ml of He were inhaled at 0.5 liter per sec from functional residual capacity. Different symbols represent different subjects. Slopes are most positive after intercostal (IC) inspiration, most negative after abdominal (Ab) inspirations, and intermediate after normal (N) inspirations.

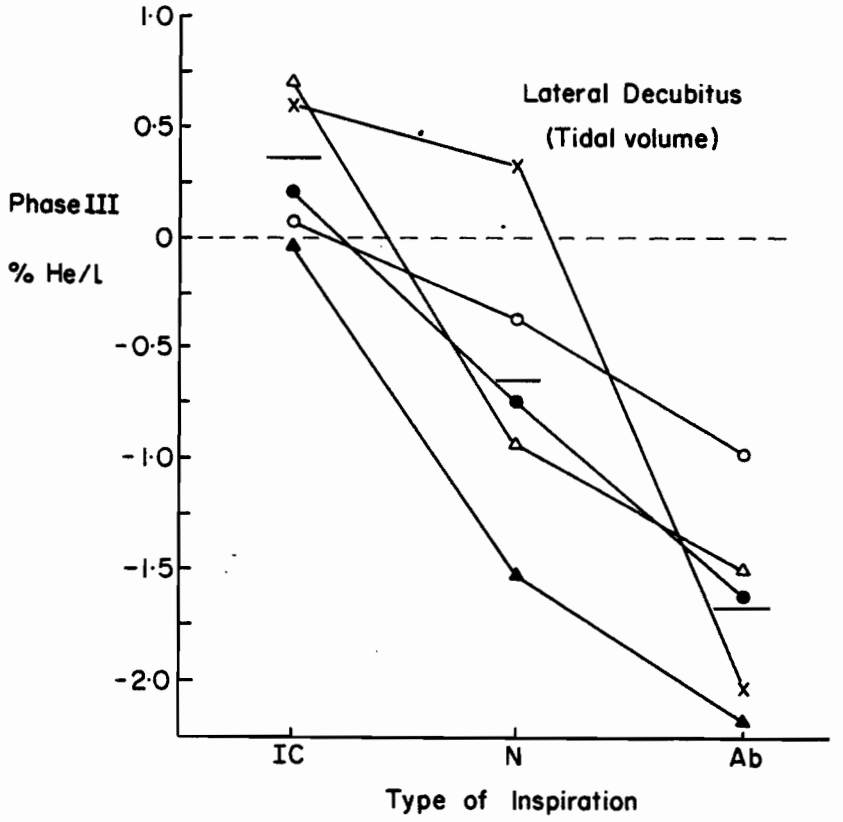

Figure 8: Influence of pattern of inspiration on slope of helium (He) plateau in lateral decubitus posture; 600 ml of He were inhaled at 0.5 liter per sec from functional residual capacity. Different symbols represent different subjects. IC = intercostal inspiration, N = normal inspiration, Ab = abdominal inspiration.

of He (150 ml) also showed differences reflected in the slope of the alveolar plateau (Fig. 9), that after intercostal inspiration (0.31 ±0.11 per liter), being greater than that after abdominal inspiration (-0.37 ±0.11 per cent He per liter; $P < 0.05$).

ii) Inspiration from RV. In both upright and supine postures there were no significant differences in the He bolus washouts among intercostal, natural, and abdominal inspirations. In contrast, in the right lateral decubitus position, substantial differences in the configuration of the He bolus washout were present between intercostal and abdominal inspirations. Because of the alinearity of the washouts, we quantified the differences in distribution by taking the difference in $F_{E_{He}}$ between 75 and 25 per cent of VC (Fig. 10). After an intercostal inspiration, this difference was greater (1.85 ±0.33 per cent He) than after an abdominal inspiration (0.75 ±0.28 per cent He; $P < 0.01$).

e) Discussion

The results of the ^{133}Xe experiments clearly show that in upright subjects the distribution of inspired gas may be altered from that during a natural inspiration by voluntary changes in the pattern of respiratory muscle contraction. We have drawn the same conclusion from the results of experiments using He as the tracer gas. The interpretation of the latter is as follows. During a slow VC expiration from TLC, in the 3 postures studied, lung regions distributed vertically

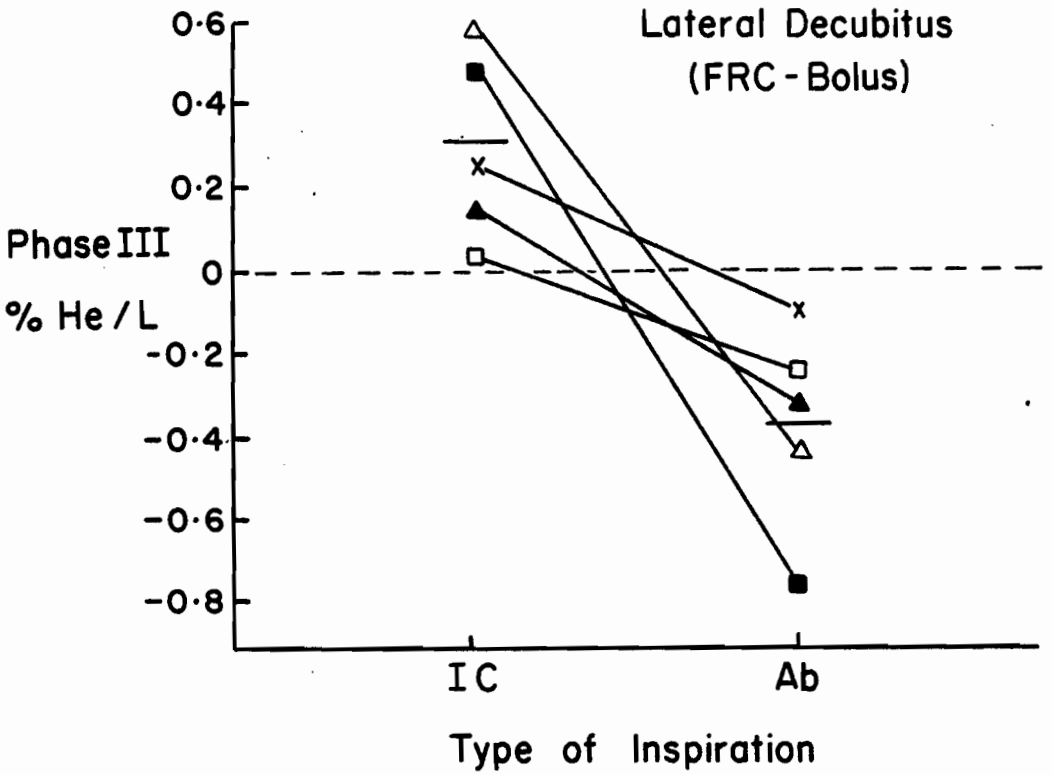

Figure 9: Influence of pattern of inspiration on slope of helium (He) plateau in lateral decubitus posture; 150 ml of He were inhaled at < 0.5 liter per sec from functional residual capacity (FRC). Different symbols represent different subjects. IC = intercostal inspiration, Ab = abdominal inspiration.

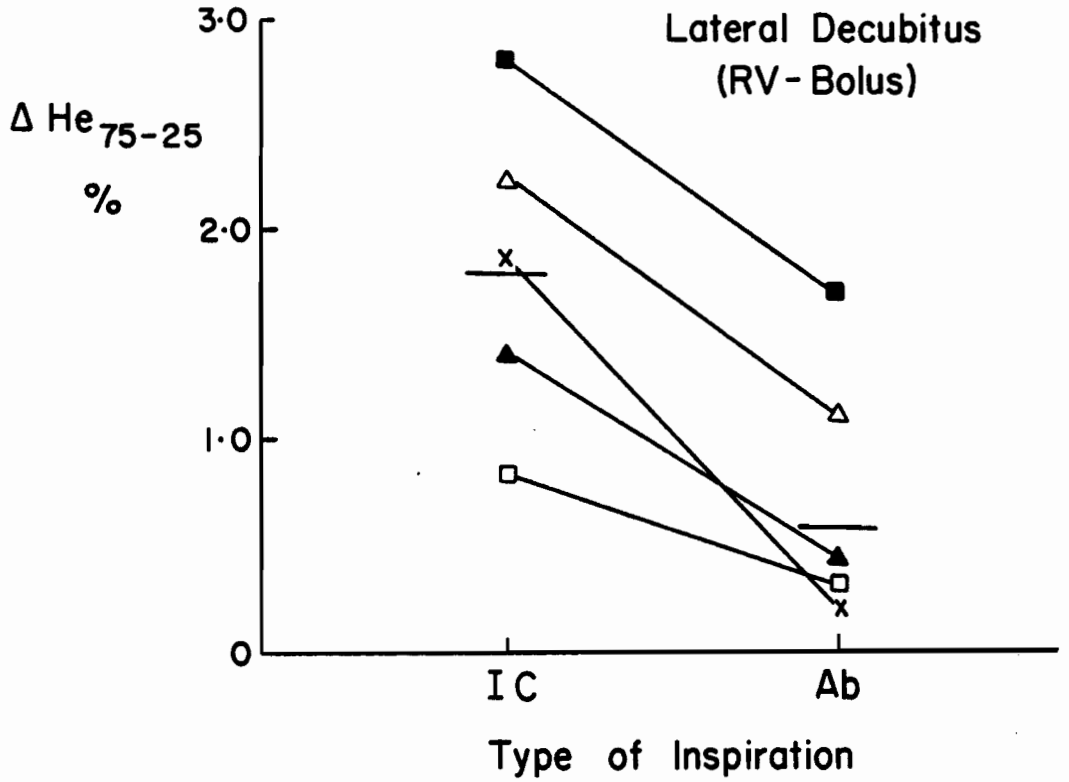

Figure 10: Influence of pattern of inspiration on the difference in helium concentration (He_{75-25}) between 75 and 25 percent of the vital capacity of the alveolar plateau; 150 ml of He were inhaled at < 0.5 liter per sec from residual volume (RV). The decrease in He_{75-25} after abdominal (Ab) inspiration reflects a more even distribution of the bolus. IC = intercostal inspiration.

in the gravity field empty sequentially, such that the dependent zones empty preferentially at high lung volumes, whereas nondependent zones empty preferentially at low lung volumes (82, 138). Thus, an upward-sloping alveolar plateau suggests higher concentrations of the tracer gas in nondependent lung regions, whereas a downward-sloping plateau indicates higher concentrations in dependent regions. Although intraregional inhomogeneity contributes substantially to the slope of the plateau (139,140), we assumed that changes in the slope produced by different muscle contractions during inspiration do not change the intraregional component. This is reasonable, because voluntary changes in the shape of the chest wall are unlikely to alter mechanical properties within small lung regions. Furthermore, because the expiration in our experiment was always the same in terms of flow, sequence of thoracoabdominal motion, and changes in diaphragmatic tension (as reflected in Pdi), differences in the slope of the alveolar plateau should have been due to different distributions of the inspired He. Indeed, in the upright posture the changes in distribution of inspired He boluses, as inferred from the washouts, matched qualitatively the changes in distribution of ^{133}Xe boluses, measured directly with external chest counters.

Our results indicate therefore that in all postures studied, gas distribution may be voluntarily altered without changing flows. An inspiration from FRC, during which mainly intercostal muscles are used, increases the distribution of

gas to nondependent lung regions. An inspiration during which abdominal motion is enhanced increases distribution of inspired gas to dependent lung zones. Natural inspirations generally produce an intermediate distribution pattern, more similar to that of abdominal breaths than to that of intercostal inspirations. These observations are true both in the upright and in the horizontal postures and apply to V_T as well as boluses of gas. Gas inspired from RV is preferentially distributed to nondependent regions in all postures, and only in the lateral decubitus position were we able to change measurably the distribution by different patterns of muscular contraction.

For understanding the topographic distribution of gas inspired at low flows, the model proposed by Milic-Emili (61) as described in Chapter II. 1, has been very useful. In this model the lung is assumed to be subjected to an essentially linear vertical gradient in pleural pressure in the gravity field. Indeed, some direct measurements in animals support this assumption (77).

Our results do not invalidate the usefulness of this model; however, they strongly suggest that changes in pleural pressure need not be the same over the whole surface of the lung but may differ systematically over different lung regions. Because flows were kept low, the different gas distribution is unlikely to have been caused by changes in regional resistances or time constants. We therefore conclude that the voluntarily induced shape changes in the chest wall influenced the distribution of the inspired tracer

by increasing or decreasing the regional pleural pressure. This is a departure from the model in which topographic gas distribution at low flows depends solely on regional pulmonary compliance. The conclusions are consistent with previous observations that Mueller maneuvers performed at FRC, using predominantly intercostal muscles, increase the esophageal pressure gradient, whereas similar mouth pressures (-15 cmH_2O), achieved by contracting predominantly the diaphragm , produce no change or a decrease in the gradient (113).

Our conclusions are also consistent with observations made in animal experiments. Electrophrenic stimulation in dogs results in more markedly negative pleural surface pressures over the lower lobes than over the upper lobes both in head-up and horizontal postures (110,111) . In contrast, after phrenicotomy, pleural pressure during spontaneous breathing is greatest over the upper lobes (110).

The effect of voluntary contraction of different respiratory muscles on the distribution of inspired gas to upper and lower lung regions is shown schematically in Fig. 11. The solid lines represent the regional volumes at different overall lung volumes, when the latter are achieved in a natural manner (after Milic-Emili, 61). The dashed lines represent the regional volumes during an intercostal inspiration from FRC. The change in shape of the chest wall due to selective contraction of intercostal muscles occurs predominantly in the volume range ac and bd. If the shape change is maintained during the remainder of the inspiration, the regional volumes

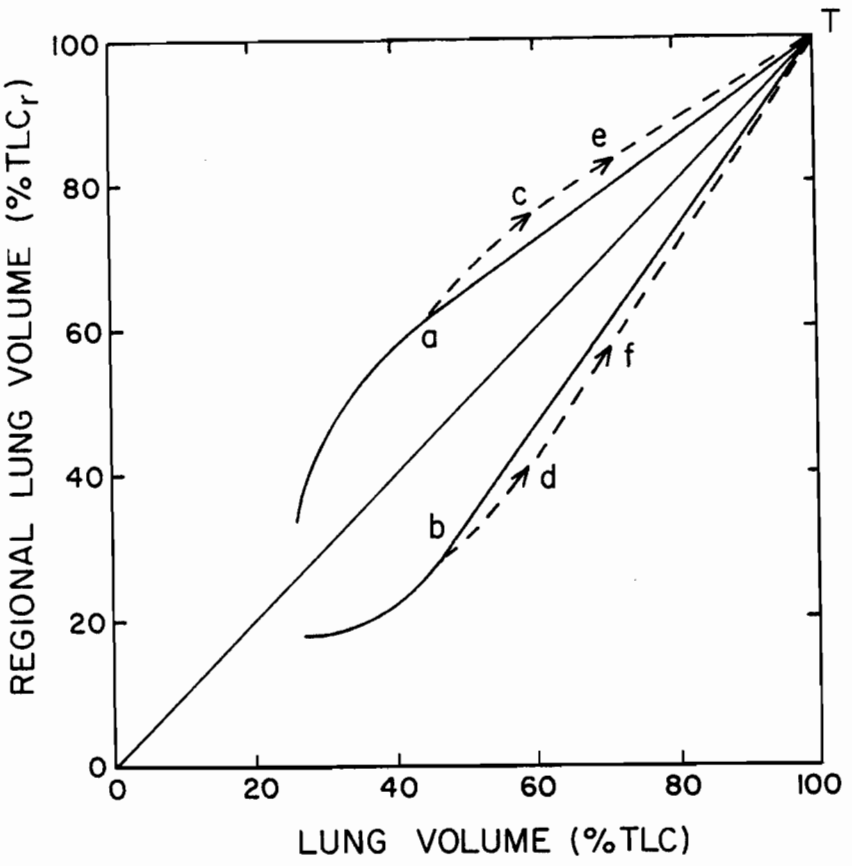

Figure 11: Two-compartment model representation of upper and lower lung regional volumes relative to overall lung volume, after Milic-Emili (61). Solid lines represent regional volumes during a natural inspiration; broken lines, regional volumes during an inspiration with the intercostals; diagonal solid line, line of identity. Arrows ac and bd show the change of regional volume during a bolus inspiration. Arrows ace and bdf show the change of regional volume during a tidal volume. (See Discussion for details). TLC = total lung capacity.

are represented by ceT and dfT. A bolus of tracer gas inhaled from FRC will be inspired in the first part of the range ac and bd, and will be more evenly distributed to the 2 lung regions than during a natural inspiration (solid lines). The inspiration of a tidal or larger volume of tracer gas may be considered as occurring in 2 stages. During the first part, ac and bd, the upper region receives more and the lower region less of the inspirate relative to the corresponding volume change during a natural inspiration. During the second part, ce and df, the lower region receives relatively more and the upper region relatively less. Thus, the greater apicobasal gradient in tracer gas concentration achieved early in inspiration decreases during the second part of the inspiration. Predictably, the greater the second part of the inspiration or the larger the breath, the smaller is the effect of the shape change due to an intercostal inspiration on gas distribution. A similar reasoning applies to an abdominal breath. This explains the smaller influence of the different patterns of inspiration on the distribution of a V_T of tracer gas than on a bolus of the tracer.

From this analysis, it is apparent that for shape changes causing even very small alterations in regional volume, distribution of a bolus of tracer gas only during the shape change is a sensitive detector of this change. The fact that Grassino and co-workers (106) observed no change in the apicobasal distribution of regional volume in upright man during a variety of submaximal shape changes is consistent with this hypothesis.

Grassino and co-workers (106) , however, limited chest wall deformation to those that would not exceed one degree of freedom. We placed no such restriction on the subjects, so that the deformations during our experiments may have been more extreme. A similar explanation may account for the difference in our results from those of Bake and associates (107). Furthermore, the exact nature of shape changes may be important. Although Bake and associates (107) did not provide details of chest wall configuration in the study cited, in a study by Grimby and associates (116) the subjects augmented abdominal breathing predominantly or exclusively in the expired direction. This differs from the enhanced abdominal motion of our subjects, which was entirely in the inspiratory direction (Fig. 2).

Although the results of our studies in upright subjects do not prove that pleural pressure swings are unequal during natural inspirations, other evidence suggests that this may be so, at least in some subjects. Direct measurements of pleural pressure in man during quiet breathing showed that the swing of pleural pressure at the lung bases is greater than that over the upper lung zones (69). Sybrecht and associates (141) calculated that very small differences in pleural pressure are sufficient to substantially alter the distribution of inspired gas. Indeed, in some persons, quasi-static distribution of ^{133}Xe boluses departs substantially from that predicted from regional pulmonary

compliances (24). The calculation is made from the subjects' regional volume distribution and the V-P curve of the lung (61).

Surprisingly, there are no published studies of the effect of voluntary shape changes of the rib cage and abdomen on the vertical distribution of regional ventilation in horizontal postures. In the upright posture, the relative stiffness of the human rib cage may explain the rather small changes in the apicobasal distribution of gas inspired at FRC, as well as the minute changes in inferred pleural pressure gradient secondary to external deforming forces applied to the rib cage (106, 108). Indeed, in some studies, substantial external force did not measurably alter the apicobasal distribution of regional volume (106) or of ventilation (Bake , B., Dempsey, J., and Grimby, G.: Personal communications). These results contrast with those in rabbits and dogs, in which externally induced deformation of the thoracoabdomen altered the gradient in pleural pressure (75), in alveolar size (64) and, by inference, in gas distribution; however, the stiffness of the human rib cage may have little bearing on the vertical distribution of gas or of pleural pressure in the supine subject. Here, it is the diaphragm that constitutes a vertical boundary, and its stiffness is variable, depending on its tension. At end-expiration the hydrostatic gradient of pressure in the abdomen deforms the relaxed diaphragm such that the dependent parts are displaced relatively more into the thorax. Consequently, the vertical gradient of regional distension reflects to some

degree the abdominal hydraulics. During an intercostal inspiration, inflation of the dependent regions is opposed by the greater hydrostatic pressure in the abdomen. At FRC the elastic recoil of the nondependent, more expanded lung regions may be less than that of the diaphragm-abdomen over the dependent lung zones. Consequently, gas distribution is preferentially to the nondependent regions, as shown in this study. During an abdominal inspiration, the dependent part of the diaphragm moves more, probably due to its greater initial length and smaller radius of curvature. Furthermore, contraction of the diaphragm turns it into a relatively rigid partition that effectively isolates the thorax from the abdominal hydrostatic pressure gradient. Both of these mechanisms result in a greater expansion of dependent lung regions and consequently, a basal distribution of inspired gas (Fig. 7).

The concept described is similar to that arising from comparison of diaphragmatic motion during spontaneous breathing with that during artificial ventilation of anesthetized and paralyzed subjects (114). Similarly, a parallel may be drawn with the differences in regional distribution of inspired gas between awake, spontaneously breathing subjects, and paralyzed artificially ventilated subjects (122). In fact, our results suggest that the different distribution of inspired gas in anesthetized paralyzed subjects is entirely explicable on the basis of chest wall mechanics and, in particular, diaphragmatic tension.

All of these considerations also apply to the lateral decubitus posture, in which, due to the greater vertical height of the thorax, the abdominal and pleural pressure differences are magnified. Indeed, the largest voluntary changes in gas distribution were seen in this posture (Figs. 8 and 9). In addition, the weight of the mediastinum probably acts to deflate the dependent lung. During an intercostal inspiration, inflation of the dependent lung is impeded by the weight of the mediastinum as well as by the hydrostatic pressure in the abdomen. Hence, the inspired gas goes preferentially to the upper lung. During an abdominal inspiration, the contracting diaphragm tenses the mediastinum, elevating it (121; see Chapter II, 2.1., Fig. 11) so that the dependent lung is expanded. Together with the greater motion of the dependent hemidiaphragm, this results in preferential distribution of inspired gas to the dependent lung.

If the lung deformations due to different patterns of respiratory muscle contraction were transient, occurring only at the onset of each breath, a bolus of tracer gas could be distributed differently but without any measurable change in the distribution of a V_T. It was to test this hypothesis that we also studied the distribution of V_T of 500 to 600 ml. During inspiration of 500 to 600 ml of ^{133}Xe-labelled gas, the tracheal detector indicated ^{133}Xe in the first 800 ml of gas flowing past in the trachea. Nevertheless, measurable differences in regional distribution were observed after different types of inspiration (Fig. 4).

This suggests that differences in pleural pressure must have been maintained during a major portion of the tidal breath.

In contrast to breaths taken from FRC, the boluses inspired at RV were distributed to apical lung zones in seated subjects. Furthermore, different patterns of respiratory muscle contraction failed to alter gas distribution measurably; however, we did notice that tracer gas distribution was very sensitive to the lung volume at which the bolus was inhaled. Inspiration of the latter from a lung volume only slightly greater than RV substantially decreased the preferential distribution to the apex. Our results are consistent with the findings that regional volume distribution is less sensitive to external deforming forces at RV than at FRC (108). Presumably, the contracted rib cage and diaphragm/abdomen musculature result in a stiffer chest wall that is less deformable than that at FRC. Furthermore, at RV the lung itself may be less deformable due to airway closure. Conceivably, greater deformations due to increased efforts, especially in subjects with less extensive airway closure, could result in different distributions. This may account for the differences observed in some subjects (117,119).

In the horizontal posture subjects were unable to alter bolus distribution at RV when supine, but measurable changes were observed in the lateral decubitus posture. Although bolus distribution at RV was always greater to non-dependent lung regions, during abdominal inspiration the distribution became more even (Fig. 10). Presumably, the voluntary redistribution of inspired gas at RV in the lateral

posture was related to the large hydrostatic pressure gradient in the abdomen and the subjects' ability to alter the shape of the 2 hemidiaphragms.

Different patterns of breathing (36, 38, 39) have been advocated without objective evidence that distribution of inspired gas may be altered. Indeed, several studies have shown that at FRC the conventional breathing patterns advocated by physical therapists do not alter the distribution of inspired gas either in patients with chronic obstructive pulmonary disease (116,117) or in normal subjects (107, 119). The results of this study show that in normal subjects certain clearly specified patterns of respiratory muscle contraction can distribute inspired gas differently in all postures. Furthermore, these patterns of inspiration were relatively easy to achieve, and none of the subjects had much difficulty in mastering the required maneuvers in 10 to 15 mins of training. We believe that these studies are important, because they potentially place a specific physiotherapeutic approach on a valid scientific basis. Application of these approaches to patients with various types of lung disease as well as to normal subjects exposed to high-gravity fields may constitute a valuable preventive and/or therapeutic measure that needs evaluation.

CHAPTER III

RESPIRATORY MUSCLE FATIGUE

...καί πνεῦμα πυκνότερον γένοιτ' ἄν· κακόν δέ τοῦτο· ξηραντικόν τε γάρ πνεύμονος καί κοπῶδες ὑποχονδρίων καί ἤτρου καί φρενῶν.

Ἱπποκράτης

...and the ventilation increases excessively. This is harmful because it dries the lungs, causes discomfort in the hypochondria and hypogastrium and fatigues the diaphragm.

Hippocrates

III. 1. Review of the Literature

The word "fatigue" has been widely used by psychologists, clinicians, and physiologists. Despite an extensive investigation on "fatigue" over the past century, it is still difficult to find a commonly acceptable definition of "fatigue", and practically impossible to find a common agreement on the mechanism and location of "fatigue". In this literature review, I will emphasize those articles which have made major advances on this subject and those which point out the complexity of the problem.

III. 1. 1) Site of Fatigue

We will define "fatigue" as the failure to generate the required or expected force during sustained or repeated contraction (142). The site where the changes responsible for the failure to generate force occurs can be theoretically located either in the central nervous system (central fatigue) or in the periphery (peripheral fatigue), involving perhaps the neuromuscular junction, the excitation-contraction coupling and/or the metabolic and energetic aspects of the muscle. The most extensive early experiments regarding the localization of voluntary fatigue were performed by Reid (143). He measured voluntary fatigue of the flexor sublimis digitorum during rhythmic isotonic and isometric contractions and compared the force of contractions of the muscle with that observed during indirect (median nerve) and direct stimulation. The initial contraction force of

maximum voluntary stimulation was identical to that obtained with artificial stimulation. However, after a period of time when voluntary fatigue was complete (practically zero force), artificial stimulation produced sizable force output and in some instances identical to the initial one. Thus, Reid located the site of fatigue primarily in the CNS, a conclusion that previous workers (144,145,146,147) had also reached, without specifically excluding transmission fatigue and muscular fatigue as contributing factors. Fatigue, in the mind, or at least in the CNS was supported more recently by Bigland-Ritchie et al (148). They compared the force of voluntary contractions of the quadriceps with electrically stimulated contractions in well-motivated subjects and concluded that "central fatigue" explained their results.

In contrast to these reports are the results of Merton in 1954 (149). He tested the adductor pollicis. He chose this muscle to be tested since it is the only one supplied by the ulnar nerve, thereby providing confidence that it can be excited by voluntary as well as electrical stimulation. Thus, he compared maximum voluntary tension of the adductor pollicis in man with maximum tension developed on electrical stimulation. He found that the fall in twitch tension was identical in both situations during a maximum static contraction leading to fatigue in several minutes. Merton thus concluded that fatigue is peripheral. Furthermore, he did not consider transmission fatigue as a possibility because the amplitude of muscle action currents of maximal electrical shocks superimposed on the maximum

voluntary contraction did not decrease throughout the experiment. Finally, Merton (150) stimulated directly the muscle with 20 mA/cm^2 and observed that the fatigued muscle did not respond whereas before the run a much weaker current had elicited a large contraction. Thus, the conclusion of Merton was that fatigue is due to the inability of the muscle fiber to respond to action currents, namely, the muscle fibers are responsible for the decline in the force output of a muscle during fatiguing work and that fatigue was not due to a transmission block of the stimulus to the muscle.

Similar conclusions that fatigue is peripheral were drawn by Naess and Storm-Mathisen (151). However, in contrast to Merton (149) they observed a decrease in the amplitude of the action currents parallel to the decrease in contraction force.

Different results were obtained by Ikai et al (152) performing the same experiments as Merton on the identical muscle except that the stimulation of the nerve was more central. They found that the force of contraction diminished faster with voluntary contractions than with contractions elicited by electrical stimulation. Evidently, the difference of the force output generated in the two situations increased with the development of fatigue. The authors concluded that the difference in their results from the findings of Merton (149,150) and Næss and Storm-Mathisen (151) is probably due to a different location of the stimulating electrode. One can argue that it may well be due to the decrease in the neural drive due to psychological reasons, since in other

motivated subjects (149,151) such a discrepancy does not exist. Furthermore, they concluded that the increasing difference between force output with voluntary as opposed to electrically stimulated contraction, reflects central nervous system fatigue. The fact that the force output of contraction with electrical stimulation also declined throughout the experiment implies peripheral fatigue as well.

The importance of peripheral fatigue was emphasized finally by Merton's experiments under ischaemic conditions(149). He observed that ischaemia produces a faster decrease in the force and recovery is delayed. This finding led him to conclude further that only peripheral fatigue exists.

Edwards and his associates (142) most recently produced impressive work showing that peripheral fatigue can assume two forms according to the response to a stimulus of low and high frequencies ("low" frequency fatigue and "high" frequency fatigue). Edwards et al (153) produced fatigue experimentally at low frequencies of stimulation, although the maximum tension achieved with high frequency stimulation was essentially unchanged. The authors hypothesized that this "low" frequency fatigue is due to alteration in excitation-contraction coupling with less force per membrane action potential. Clinically, this impairment in excitation-contraction coupling is thought to cause the weakness of familial hypokalaemic periodic paralysis (154) and of some forms of myotonia (155). Similarly, fatigue may be obtained at high frequencies while the maximum force output is intact at low frequencies (142). The primary block in "high"

frequency fatigue is hypothesized to be at the neuromuscular junction observed clinically as occurring in myasthenia gravis, myotonia (156), partial curarization (156) and during ischaemia (142).

III. 1. 2) · Histochemical Basis of Fatigue

The histochemical, biochemical and physiological characteristics of muscle fibers have been greatly studied in the last ten years and profoundly contributed to the understanding of some of the underlying mechanisms of fatigue. Burke et al, in 1971 (157) opened a new era in the pathogenesis of fatigue using intracellular micropipettes to stimulate individual motor units in cat gastrocnemius. They identified motor units in which some muscle fibers fatigued rapidly, some fatigued slowly, and some did not fatigue at all. Biochemical characteristics of isolated contractile proteins (158) and contractile properties of motor units (157) support the identification of fast and slow fibers based on the histochemical demonstration of myofibrillar ATPase at pH of 9.4. Furthermore, according to their oxidation capacity (mainly on succinic acid dehydrogenase-SDH), the muscle fibers are categorized as high oxidative and low oxidative (159,160). Thus, the muscle fibers can be categorized as low oxidative fast-twitch (LFT) fibers, high oxidative fast-twitch (HFT) fibers and high oxidative slow twitch (HST) fibers.

Resistance to fatigue of single muscle units (161) in cats and rats is directly correlated with the intensity of the

oxidative capacity of the fibers. Furthermore, the oxidative capacity is closely related,firstly, with the density of mitochondria in the fibers (162,163) and secondly, with the richness of fiber capillary supply (164,165). It follows that oxidative enzyme capacity as it is tested histochemically and biochemically may be the determinant of the fatiguability of the fibers. In fact, the HST and HFT are resistant to fatigue whereas the LFT are easily fatiguable. However, this distinction is not completely clear cut. The content of other oxidative enzymes and of cytochrome "C",which is another index of mitochondrial content, sometimes appears to be less in the extremely fatigue-resistant HST fibers than in HFT fibers. This is particularly so in the soleus muscle of the rat (159,166,167,168). These findings are very indicative that the oxidative enzyme capacity as it is tested today may not be the only factor which determines the resistance to fatigue. However, it is an important factor which provides a useful index of this muscular modality. Endurance training for instance does not alter the speed of contraction of the muscle (169),but the muscle becomes more resistant to fatigue and exhibits an increased number of mitochondria and increased O_2 uptake per gram net weight (170). Furthermore, the HFT fibers in chronically exercised animals have a significantly greater number of capillaries as compared to HFT fibers in sedentary animals (164). Thus, it seems likely that fibers increase their oxidative capacity and can be 'converted' by endurance training from LFT to HFT fibers. This conversion is evidently reversible over a period

of several months following cessation of exercise (171).

With regard to the diaphragm in particular,histochemical studies of this muscle in guinea pigs and humans by Lieberman et al (172) have shown that 76% of the fibers are high oxidative in type and 24% are low oxidative fibers. The authors hypothesized that the decrease in maximum voluntary ventilation (MVV) over a lengthy test period may be directly related to fatigue of LFT fibers and that the maximum sustainable MVV represents the contribution of HST fibers in the diaphragm. Keens et al (174) have also studied the fiber type composition of the diaphragm and intercostals in rats and they found 54.9% HST fibers in the diaphragm and 65.2% in the intercostals. Hence, the fact that with appropriate training the maximum sustainable MVV increases markedly (55) may suggest that the diaphragm, like other skeletal muscles, is capable of increasing its oxidative capacity. Indeed,Keens et al (174) have shown that the diaphragm and intercostals of the rats increased their oxidative capacity after imposing on the animals chronic inspiratory loads.

III. 1. 3) Metabolic Aspects of Fatigue

a) Fuel Depletion

The duration for which strenuous exercise (long distance running or bicycling) can be maintained seems likely to be determined by the concentration of glycogen in the muscles at the beginning of exercise and the rate at which the glycogen stores are depleted (175,176,177,178,179,180). Studies in which serial biopsies of the quadriceps muscle

were obtained from men performing prolonged strenuous exercise have provided evidence that the complete failure of the muscle as a force generator coincides with the depletion of muscle glycogen stores (176,178). The relation of glycogen depletion in the various fiber types during different work intensity has further increased our understanding of the patterns of muscle fiber involvement in different types of exercise and the development of fatigue.

Gillespie et al (181) have shown that HFT fibers in bushbaby (Galago senegalensis, a small lower primate) becomes depleted of glycogen prior to depletion in LFT fibers when the animal is exercised on a treadmill at a steady walk, whereas the pattern of glycogen depletion is reversed when the animal is required to move in forceful repeated leaps. In man (179,182), glycogen depletion in the vastus lateralis after submaximal bicycle exercise occurs first in HST fibers and later in LFT fibers. It is of great interest that when all fibers were depleted of glycogen at a given load the subjects were unable to continue the work at the initial level, which suggests that the loss of muscle glycogen was related to the fatigue produced in these experiments. Similar experiments at higher work loads showed an initial and more prominent glycogen depletion in LFT fibers than in HST fibers.

During prolonged exercise, the liver can provide significant amounts of glucose to the blood and glucose is taken up by active muscles (183). Baldwin et al (183) have

shown that in rats subjected to prolonged exercise, the liver may be a very important source of energy. It was observed that the liver glycogen of the rats decreased by up to 85% of the initial value after 2 hours of exercise while in the various skeletal muscles glycogen decreased to 42 - 72% of its initial value.

Changes in blood sugar during muscular work have received considerable attention by many investigators. Among the several works in this subject Bergström et al (178) found a significant drop in blood sugar during heavy aerobic work dependent on the diet while Christensen and Hansen (184) had reported earlier that acute ingestion of glucose reversed the hypoglycemia and allowed the work to be prolonged. Furthermore, Åstrand (185) observed hypoglycemic symptoms in cross country skiers after 1½ hours exercise. An interesting question that remains to be answered is whether the hypoglycemia has its primary fatiguing action in the CNS or in the muscle. Along these lines, Spande and Scholtelius (186) provided substantial evidence that the glucose level in an isolated muscle affects its performance. Decrease or removal of glucose from the bath solution of the isolated mouse soleus muscle showed that the tension developed for a given stimulus decreased but returned to baseline values after re-addition of glucose to the bath. However, regardless of the site of its action (peripheral or central) it remains important that a drop in glucose concentration is related to the failure of generating the required or expected force.

With continued, prolonged heavy work, muscles utilize their own fatty acids (183,187,188) and take up free fatty acids (FFA) from the blood. Today, it is well documented that during moderate work substantial amount of the needed energy is derived from fat as time progresses (189,190,191,192). The concentration of the FFA in the blood may increase manyfold towards the end of exercise compared to the values at the start of exercise (189,191,192), suggesting that there is a high output of FFA from adipose tissue in order to meet the energy demands of the muscle. Whether the supply of FFA ever becomes limited is questionable. Adipose tissue is a practically inexhaustible source of FFA although in some situations, such as severe and prolonged starvation and/or decreased blood flow, the supply of FFA to the muscle may potentially diminish.

Hultman, Bergström and Anderson (193), in 1967, studied the breakdown and resynthesis of phosphocreatine (PC) and adenosine triphosphate (ATP) in human muscles during heavy work. They demonstrated that at very high loads, the PC concentration decreased rapidly down to zero and the contractile capacity of the muscles ceased. Furthermore, they observed that the ATP concentration also decreased and when the level of PC is near zero the ATP drop is approximately to 40% of its initial value. The relation of PC to fatigue has also been studied in isolated mouse soleus muscles by Spande and Schottelius (186). They stimulated the muscle tetanically for 1 sec every 20 secs for 3 hours, and they found an excellent linear relationship

between the terminal isometric tension and the terminal PC concentration. Edwards et al (153) related the force of maximum voluntary contraction of the quadriceps muscle in humans to the muscle content of phosphagen at the end of static and dynamic exercises. It was observed that the force of maximum voluntary contraction was reduced to zero and to 8% in two subjects, and the muscle content of phosphagen was reduced to about 10% of the normal value. During recovery, the phosphagen was resynthesized (when the circulation was intact) in a fashion that approximately followed recovery in force (153, 194).

b) Accumulation of Lactic Acid

Lactic acid accumulation in the muscle has been considered for many years as a potential underlying cause of fatigue. Most of the evidence of this hypothesis came from the studies of Hill and Kupalov (195), who observed that the frog sartorius muscle stops contracting when the concentration of lactic acid in the muscle rises to 0.3%, corresponding to 33 μmoles/g. They maintained that fatigue appears at concentrations above 9 μmoles/g. Since then, the bibliography is enormous regarding the role of lactic acid but surprisingly, the relationship between intramuscular lactic acid concentration and muscle fatigue was not studied until recently. Fitts and Holloszy (196) attempted to determine whether there was a close correlation between lactic acid concentration and twitch tension in frog sartorius muscle. The isolated sartorius muscles were stimulated at a rate of 30 per min with supramaximal pulses while immersed in a glucose containing

Ringer's solution under anaerobic conditions. It was observed that the concentration of lactic acid in the muscles increased and the isometric twitch tension fell progressively. Furthermore, the increase in lactic acid was inversely proportional to the decrease in contractile force ($r = -0.99$, $p<0.000001$).

In the same study, the recovery from fatigue was also investigated and it was found that there was also a significant inverse correlation between lactic acid concentration and contractile force during the recovery period ($r = -0.92$, $p<0.00001$). However, recovery of contractile force lagged behind the decrease in lactate; a given concentration of muscle lactate was associated with higher contractile force early during development of fatigue rather than later during recovery. This observation led the authors to postulate that some secondary effect induced by increased lactate must persist while lactate concentration is decreasing.

The role of lactic acid to fatigue during isometric contraction (197) and during normal exercise in man has been also studied (198). Karlsson and Saltin (198) measured lactate concentration in quadriceps muscle biopsy samples and in the blood during exhausting bicycle exercise of 2, 6 and 16 minutes duration. The accumulation of lactate in the blood and in the muscle increased continuously until exhaustion. In the muscle tissue, both at the highest and medium loads, lactate averaged 16.1 m moles/Kg but only 12.0 m moles/Kg wet muscle at the lowest load. It was con-

cluded by these investigators that since the concomitant changes in glycogen and high energy phosphate which they also measured were not sufficient to explain the exhaustion of the muscle, then the concentration of lactic acid in the muscle might have been responsible for the development of fatigue for the two high loads. However, the question remains why exhaustion occurred at the lowest load with the lower lactic acid level — a question which again suggests that the mechanism of fatigue is multifactorial. Although the notion that the accumulation of lactic acid in the muscle is responsible for fatigue has great interest, the underlying mechanisms are not yet clearly known. The reduction in pH due to lactic acid accumulation may produce a decrease in the number of calcium ions bound to troponin during excitation-contraction coupling. This will result in a decrease in contractile force. Furthermore, the drop in pH inhibits the activity of phosphofructokinase, which could cause inhibition of glycolysis during intense muscular work resulting in a decrease in ATP supply (199). However, it must be stated that the available evidence that lactic acid is responsible for fatigue seems highly suggestive and very appealing, but still remains to be further proven.

III. 1. 4) Effect of Hypoxia on Muscle Endurance

Hypoxia may predispose to fatigue in isolated muscles (186) and certainly influences overall human performance (200). In the studies of Spande and Schottelius (186) in which the fatiguability of isolated mouse soleus muscles

was measured by tetanic stimulation for 1 sec every 20 secs for 3 hours, the influence of anoxia was studied by removing oxygen from the bath. The tension that the muscle was able to produce under anaerobic conditions was substantially inferior than when the muscle environment was rich in oxygen.

The maximal oxygen uptake per minute ($\dot{V}O_{2max}$) and physical performance under hypoxic conditions has been extensively studied in man. It is generally agreed that both $\dot{V}O_{2\ max}$ and maximum physical performance decrease during hypoxic hypoxia or when the oxygen carrying capacity of the blood is reduced either by inhalation of carbon monoxide (201,202) or by anemia (203), or by hemodilution (204) because the maximum cardiac output is relatively unchanged (205,206,207). It is predictable, therefore, that by decreasing the oxygen content of the blood while not increasing the cardiac output, the $\dot{V}O_{2\ max}$ and performance will decrease. However, the information that is available regarding the effect of hypoxia on endurance of a single muscle or small groups of muscles in man are scanty and conflicting. Kaijser (208) has shown that the endurance time to exhaustion during dynamic forearm work at 150% of the maximum work load which the subject could sustain for 6 minutes ($\dot{W}_{max\ 6}$) was significantly lower breathing 10% oxygen than the corresponding values obtained during air breathing ($p < .05$). Furthermore, breathing 10% oxygen he reported higher values of lactic acid in the samples of blood from the working arm at the end of exercise than when the subjects breathed air. In contrast to this result, Monod (209) did not find any differ-

ence between the endurance time of biceps during dynamic work while the subjects were breathing 8% oxygen compared to their breathing air. Differences in frequency of contraction may well account for this discrepancy. Indeed, in Kaijser's experiments the frequency of contraction was 60/min as opposed to a frequency of 10/min in Monod's experiments. Therefore, it is likely that in Monod's study, compensation of the oxygen content could have been achieved by increased blood flow to the muscle while in Kaijser's experiments such compensation could not be obtained. Increased frequency of contraction for a constant duration of contraction will decrease the time interval between contractions. This will probably decrease the blood flow to the muscle. The blood flow reaches the highest level during the intervals between contractions, while during contractions exceeding 15% of the maximal strength of the muscles, the flow is impeded (210). Thus, another factor that affects the blood flow to the muscle is the degree of contraction. It is known that there is a progressively greater interruption of blood flow to active muscles (211,212) for tensions between 15 and 70% of maximum and that at 70% of the maximum the vasculature is completely occluded. It is conceivable, therefore, that up to a certain level of frequency, duration and degree of contraction in intermittent work, the overall increase of blood flow (213,214) is such that it can meet the muscular demands even if oxygen content or other substrates are low in the circulation. However, any further increment in work will result in oxygen or fuel debt to the muscle.

The influence of hypoxia on the endurance of the respiratory muscles has not been studied extensively. There is only the work of Tenney and Reese (52) in which the investigators examined the effects of hypoxia (9% in N_2) on the endurance times at different levels of MVV, while the Pco_2 was kept constant. Comparing endurance times at the same % MVV, it appears from this study that ambient hypoxia had little, if any, effect. Furthermore, during the breathing test, Tenney and Reese's subjects performed mild exercise with the idea of depriving the respiratory muscles of some of the available oxygen, viz, by increasing the demand of the leg muscles. Comparing the endurance times at the same % of MVV, it was found that there was no difference in results obtained during room air breathing or 9% O_2 breathing.

III. 1. 5) Force-Length Relationship

Wilkie demonstrated that the maximum force that a muscle can develop is a function of its length (215). At rest, if a muscle is stretched passively it opposes the exerting stretch by an opposite force that increases slowly at the beginning and faster with increased stretch. If the muscle is fixed at the resting length (the length that it keeps in the body) and is electrically stimulated in order to produce tetanus, it develops the greatest force. This force will decrease with the same stimulus if the length of the muscle increases or decreases. However, the total force increases with large stretch, but this is due to the

large contribution of the passive tension. Most skeletal muscles shorten only to about 60% of resting length when stimulated to contract isotonically and at this length in isometric contraction they do not exert any tension. The diaphragm differs in two senses from this behaviour (216); its maximum contraction is exerted at approximately 130% of its resting length and stops developing any tension under isometric conditions, at approximately 36% of its resting length (Fig. 1).

It is explicit from the force-length relationship of the muscle, that for a given stimulation, if a given force is developed at resting length this force will decrease when the muscle length is shortened. Thus, in order to achieve the expected or required force, the stimulation has to increase. However, if the shortening is great, even supramaximal stimulation may not be sufficient to compensate for the force loss. Thus, for any given tension developed, a muscle with a shorter fiber length will require greater excitation and, therefore, greater energy consumption than a muscle with a larger fiber length.

In the respiratory system, the inspiratory muscles shorten as lung volume increases. Although we do not measure the force of the inspiratory muscles, we can measure the pressures that the muscles can develop, which can be considered as an index of their force. Thus, the relationship between maximum inspiratory pressures and lung volume is a measure of the force-length properties of the inspiratory muscles. Based on the force-length relationship,

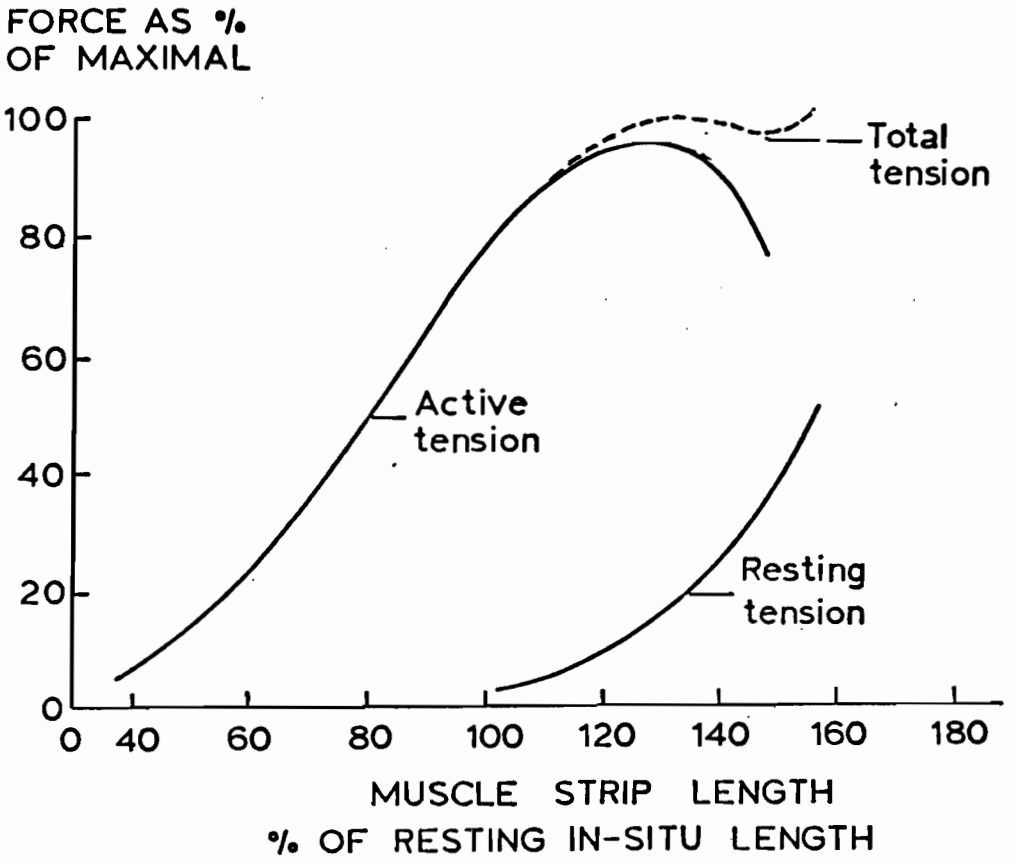

Figure 1: Diagrammatic representation of active, passive and total length-tension of the diaphragm (After Kim et al, 216). On the abscissa 100% designates resting in situ length as determined by the first appearance of passive tension. Ordinate is the force expressed as percentage of maximal active force.

the maximum inspiratory pressures should decrease as lung volume increases which, in fact, Rohrer (217) and Rahn et al (218) have shown to be the case. Furthermore, Marshall (219) showed that intrapleural pressure diminished as lung volume increased during a constant stimulation of the phrenic nerves. Similarly, Pengelly et al (220) stimulated the phrenic nerves in man and cats and found that for a given stimulus, with increasing volume, transdiaphragmatic pressure decreased at a constant inspiratory flow.

Geometric factors may also play a role for the maximum pressure volume relationship of the inspiratory muscles. As the lung volume increases, the radius of curvature of the diaphragm becomes greater and, therefore, the transdiaphragmatic pressure becomes less for a given tension. The significance of the effect of both the geometry and the lung volume on the transdiaphragmatic pressure was elegantly studied by Kim et al (216). They concluded that the influence of volume on diaphragmatic curvature and on the conversion of diaphragmatic force into pressure was much smaller than the influence of length on force. These findings indicate that the diaphragm during breathing moves caudally and cephally like a piston, preserving more or less its geometry. The effect of the chest wall geometry on the relationship of diaphragmatic activity and pressure developed was studied by Grassino et al (221) for a constant volume at different thoracoabdominal configurations. They showed that at the same lung volume, for a given electromyogram of the diaphragm (Edi), Pdi increased as volume was displaced from

the abdominal compartment to the rib cage compartment. They explained it by the lengthening of the diaphragm and/or changes in diaphragmatic curvature. They concluded that volume is only a very approximate index of diaphragmatic length. Conceivably, for any change in volume with a given Pdi, the average energy expenditure will be different depending on the length and curvature of the diaphragm.

In the context of the force-length relationship, an important question arises. Does a muscle fatigue faster at a given tension or at a given percentage of the maximum tension as its length shortens? I was unable to find a study that dealt with this question in either the English or the French literature. However, some predictions may be drawn. If a muscle fails as a force generator at a given percentage of the maximum strength and this percentage remains constant at all lengths, it is conceivable that a given force may not be fatiguing at resting length but it may well be fatiguing at a shorter length. The energy demands at shorter lengths will be higher and may well exceed the energy supply.

III. 1. 6) A Muscle as a Mechanical Model

A muscle consumes chemical energy and generates mechanical energy work. Therefore, a muscle is an engine. The direct source of energy in the muscle is adenosine triphosphate (ATP) which during contraction splits into adenosine diphosphate (ADP) and phosphoric acid . A muscle , however, contains only very small quantities of ATP. Thus, after a few contractions it would exhaust its

supply and would stop contracting if ATP were not continuously resynthesized. The resynthesis of ATP needs energy, the most direct supply of which is creatine phosphate (PC). The amount of PC in muscle is greater than ATP but even so, the total store of energy in a muscle is not large enough to provide for prolonged activity. Creatine phosphate, in the process of restoring ATP, is split into creatine and phosporic acid. Thus, if muscular activity is to be prolonged, it is necessary that phosphagen (ATP+PC) be continuously resynthesized. The resynthesis of phosphagen requires energy which is supplied to the system via two fundamental reactions: combustion of food and glycolysis (222,223). It has been hypothesized (149,224) that fatigue results from a depletion of phosphagen and that phosphagen depletion takes place when its consumption occurs at a rate faster than its resynthesis. However, even if this process is not as simple as is energy depletion, it is generally considered as an underlying one in the development of muscle fatigue (142). It is possible, therefore, that the energetic process of the muscles regardless of their complexity can be represented in a simplistic form with various mechanical models, the usefulness of which is to understand better the physiological events and to make predictions and test them.

Margaria (223) has proposed an hydraulic model of the energetic processes in muscles shown in Fig. 2. The fluid in vessel P (representing phosphagen) is directly connected to the outside through the tap T, which can control the flow

which represents energy expenditure. When this tap is closed, the upper level of fluid in P is the same as in the communicating reservoir of O_2 which has infinite capacity. This reservoir is the source of oxidative energy. When the tap allows liquid from vessel P to flow outside (energy expenditure or phosphagen breakdown), the level of fluid in P will fall. At the same time, fluid from vessel O_2 flows to vessel P since the level of the fluid in vessel O_2 is higher than the level in vessel P. If energy expenditure is not very high (low flow through the tap T), the level in vessel P will be lower than at rest, but will reach an equilibrium value as fluid continuously flows from vessel O_2 through the resistance R_1. The flow through R_1 (corresponding to the oxygen consumption $\dot{V}O_2$) will depend on the pressure difference between the two vessels (O_2, P) which in turn will depend on the flow through the tap (rate of energy consumption). However, when there is a high rate of energy consumption (the tap is open so wide that the flow through T is higher than through R_1), the level in P falls below the level of R_1. In this case, the flow of liquid from vessel O_2 to vessel P reaches a constant maximum value (maximum oxygen uptake, $\dot{V}O_{2\ max}$) which is independent of the level in vessel P. Under these circumstances, $\dot{V}O_2$ is only determined by the height of the fluid in O_2 and by the resistance of R_1. The decrease of the level of the fluid in vessel P below R_1 produces influx into vessel P from the vessel LA (lactic acid formation) through a resistance R2 and a one-way

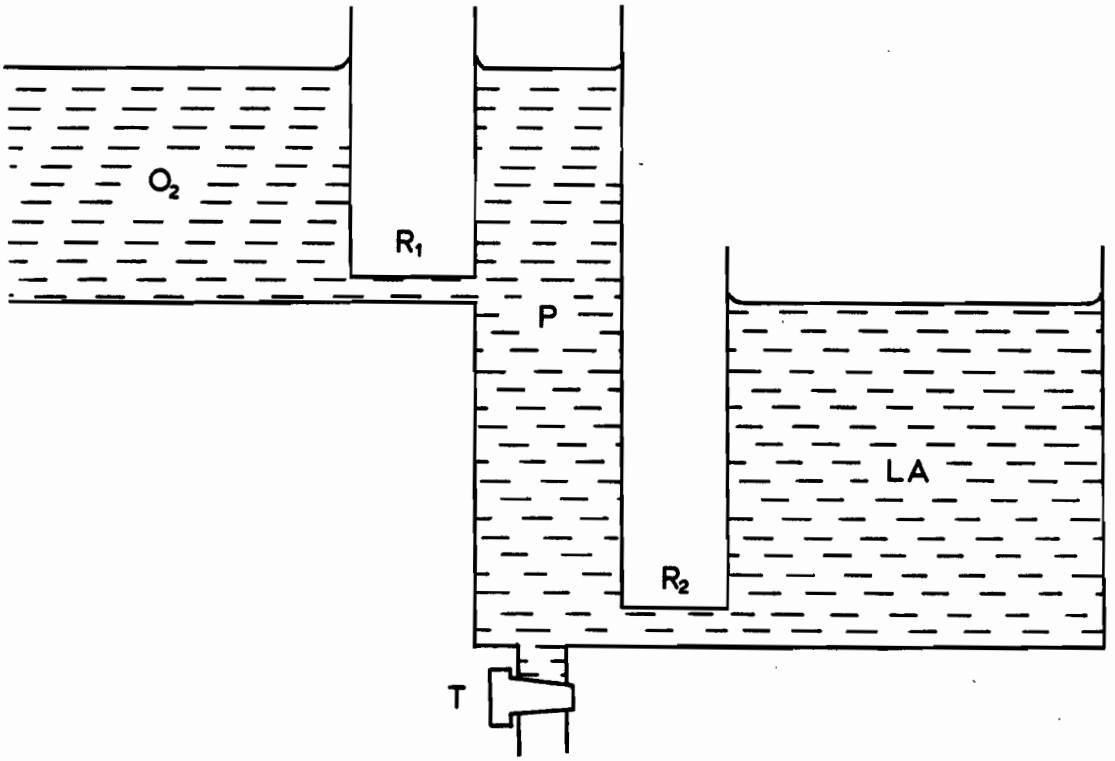

Figure 2: A hydraulic model of energy sources in muscular activity (223). (For explanation see text).

valve allowing flow from vessel LA to vessel P only. The flow from vessel LA to vessel P will be regulated according to the different levels of fluid in the two compartments (P, LA) and to the resistance of the communicating channel R_2. If the flow through T is not extremely high, a steady level of the fluid in vessel P can be obtained below the level of R_1, but only for a limited time because the container LA only has a finite capacity. After a while, due to the decreased level of fluid in vessel LA, the new steady condition will be disrupted and as vessel P empties, vessel LA will become nearly empty and tap T will suddenly shut (time of exhaustion). If tap T is fully opened (maximum energy consumption), the resistance R_2 though lower than the resistance R_1, is higher than the resistance of tap T when fully opened, so that maximum flow through T cannot be maintained even if a large amount of fluid exists in vessel LA. Again vessel P will sooner or later become empty and tap T will shut (exhaustion). This model, despite its complexities does not deal with all energetic factors in details. For example anaerobic energy appears in this model after the $\dot{V}O2_{max}$ is reached while in reality anaerobic metabolism appears before $\dot{V}O2_{max}$.

Based on experimental findings obtained during dynamic work of biceps and quadriceps muscles at different levels of intensity, Monod and Scherrer (225) stated that the total energy (C) consumed during work, leading to exhaustion at a given period of time (t_{lim}) is equal to the rate of energy supply to the muscle (β) times the total time of work (t_{lim}) and to the energy stored in the muscle (α).

$$C = \alpha + \beta t_{lim} \quad (1)$$

or $$\dot{C} = \frac{\alpha}{t_{lim}} + \beta \quad (2)$$

or $$t_{lim} = \frac{\alpha}{\dot{C} - \beta} \quad (3)$$

where $\dot{C}$ = rate of energy consumption.

In the analysis of Monod and Scherrer, α is equivalent to the fluid of vessel P (phosphagen) and β to the flow from the vessels O_2 and LA of Margaria's model.

This mathematical model (Eqs. 1-3) is a unifying concept. It explains why fatigue is well-correlated with so many different things and it becomes helpful in approaching and examining the phenomenon of fatigue in at least some circumstances. Thus, we will analyse our findings in the light of this mathematical model, which will be commented upon in detail in the following discussions.

III. 2. Experiments

III. 2. 1) Diaphragmatic Fatigue in Man

a) Summary

The time required (t_{lim}) to produce fatigue of the diaphragm was determined in three normal seated subjects, breathing through a variety of high, alinear, inspiratory resistances. During each breath in all experimental runs the subject generated a transdiaphragmatic pressure (Pdi) which was a predetermined fraction of his maximum inspiratory Pdi (Pdi_{max}) at functional residual capacity (FRC). The breathing test was performed until the subject was unable to generate this Pdi. The relationship between Pdi/Pdi_{max} and t_{lim} was curvilinear so that when Pdi/Pdi_{max} was small, t_{lim} increased markedly for little changes in Pdi/Pdi_{max}. The value of Pdi/Pdi_{max} that could be generated indefinitely (Pdi_{crit}) was around 0.4. Hypoxia appeared to have no influence on Pdi_{crit}, but probably led to a reduction in t_{lim} at $Pdi > Pdi_{crit}$ for equal rates of energy consumption. Insofar as the behaviour of the diaphragm reflects that of other respiratory muscles, it appears that quite high inspiratory loads can be tolerated indefinitely. However, when the energy consumption of the respiratory muscles exceeds a critical level, fatigue should develop. This may be a mechanism of respiratory failure in a variety of lung diseases.

b) Introduction

Respiratory failure is attributed in most instances to lung disease, alteration of ventilatory control mechanisms,

or neuromuscular disorders. An important question is whether or not respiratory muscle fatigue can cause respiratory failure due to lung disease when the system must overcome resistive or elastic pulmonary loads, or due to neuromuscular disease when the muscles are weakened. Although it has been speculated that respiratory failure in some conditions (e.g., asthma) might be due to fatigue, the existence of respiratory muscle fatigue as a cause of respiratory failure has never been substantiated.

Clark et al (226) showed that in patients with certain types of pulmonary diseases,ventilation limits exercise. However, the role of respiratory muscle fatigue has not been delineated. Moreover, Freedman et al (53) questioned whether respiratory muscle fatigue can ever limit the performance of exercise in athletes. Yet Tenney and Reese (52) demonstrated that the maximum indefinitely sustained ventilatory level is around 55% of maximum breathing capacity, which is close to the ventilation seen in maximum tolerable steady-state exercise (53). At higher levels of ventilation,Riley (227) and Ouellet et al (228) have postulated that the "cost of breathing would dominate the total cost of tissue maintenance" and could be considered the limiting factor of exercising muscles.

The purpose of this study was to investigate the dynamic performance of the diaphragm at various rates of work under normoxic and hypoxic conditions to determine the time required to produce diaphragmatic fatigue, and hence to estimate the maximum pressure the diaphragm can produce

indefinitely without becoming fatigued. In this way we hoped to produce information relevant to the role of respiratory muscle fatigue in respiratory failure and in exercise limitation.

c) Methods

Three normal male subjects were studied in the sitting position at functional residual capacity (FRC). Constancy of end-expiratory lung volume was monitored by observing end-expiratory transpulmonary pressure. The subject breathed through a Hans-Rudolf valve (Fig. 1). The inspiratory inlet of the valve was connected with a small rubber tube on which different resistances could be applied during inspiration. Expiration was performed without added resistance. All resistances were alinear and varied from 50 to 200 $cmH_2O/l/s$ The different resistances helped the subject achieve a predetermined fraction of his maximum inspiratory transdiaphragmatic pressure (Pdi_{max}) at FRC with each breath. Transdiaphragmatic pressure (Pdi) was defined as the difference between gastric and esophageal pressures. These were measured by means of two thin-walled latex balloons (5 cm long and 3 cm in circumference) one positioned in the stomach and the other in the middle third of the esophagus. The gastric balloon was connected by a polyethylene catheter and a Y-tube to one side of each of two pressure transducers (Sanborn 267B). The esophageal balloon was connected by a polyethylene catheter and a Y-tube to the other side of one of the transducers to which the gastric balloon was connected, and to a third

pressure transducer. To prevent unpleasant sensations during the run due to irritation of the pharynx and the nasal mucosa by the polyethylene tubes, a local anesthetic (Xylocaine 2%) was applied to the oro- and nasopharynx before each experiment. A fourth pressure transducer was connected through a polyethylene tube with the mouthpiece. The first transducer measured gastric pressure (Pg), the second recorded Pdi, the third esophageal pressure (Ppl), and the fourth measured mouth pressure (Pm). Except for Pdi, all pressures were measured relative to atmospheric pressure. We sampled the expired gas at the mouthpiece and measured the concentrations of CO_2 and O_2 with a mass spectrometer (Perkin Elmer). We measured flow rate with a Fleisch pneumotachograph and a Validyne differential pressure transducer whose signal was integrated to measure changes in volume. All signals were recorded on a Hewlett-Packard strip-chart recorder.

Prior to each run, the subject contracted his diaphragm maximally at FRC, by performing a diaphragmatic inspiratory effort with the upper airways closed (Mueller maneuver) generating a Pdi_{max}. The subject performed the diaphragmatic Mueller maneuver by attempting to achieve abdominal motion rather than rib cage expansion. This Pdi was very reproducible in each subject and invariably greater than the Pdi obtained at FRC during an expulsive maneuver by the same subject. Thus the value that we obtained in two subjects was 180-190 cmH_20 and in the third 275-285 cmH_20. The maximum value reported by Agostoni and Mead during an

expulsive maneuver was 200 cmH_2O (229). The subject subsequently breathed through the inspiratory resistances generating a Pdi which was a predetermined fraction of Pdi_{max}. The Pdi signal was displayed on an oscilloscope in front of the subject (Fig. 1) who attempted to sustain the predetermined Pdi throughout the whole inspiration of each breath until exhaustion. The subject was allowed to choose his own tidal volume and frequency. The end point (endurance time, t_{lim}) was determined by the time the subject could tolerate the procedure no longer and came off the mouthpiece. This occurred 2-5 breaths after he was unable to achieve and sustain the predetermined Pdi.

The experiments were done first inspiring room air and in another series, in two subjects, inspiring a mixture of 13% O_2 in N_2. In the latter experiments the subjects inspired the hypoxic mixture for 10-15 mins before the resistance was applied so as to achieve a steady-state condition. The ECG was monitored continuously during these runs.

The experiments were done in no particular order on each individual. Each subject performed one fatiguing run per day and occasionally two runs the same day (one run early in the morning and one late in the afternoon).

Since the end point could be influenced by subjective factors, motivation was a serious consideration. Therefore, the spirit of cooperation was judged to be important and competition between individuals was introduced. Furthermore, so that the subjects did not know how they were "expected"

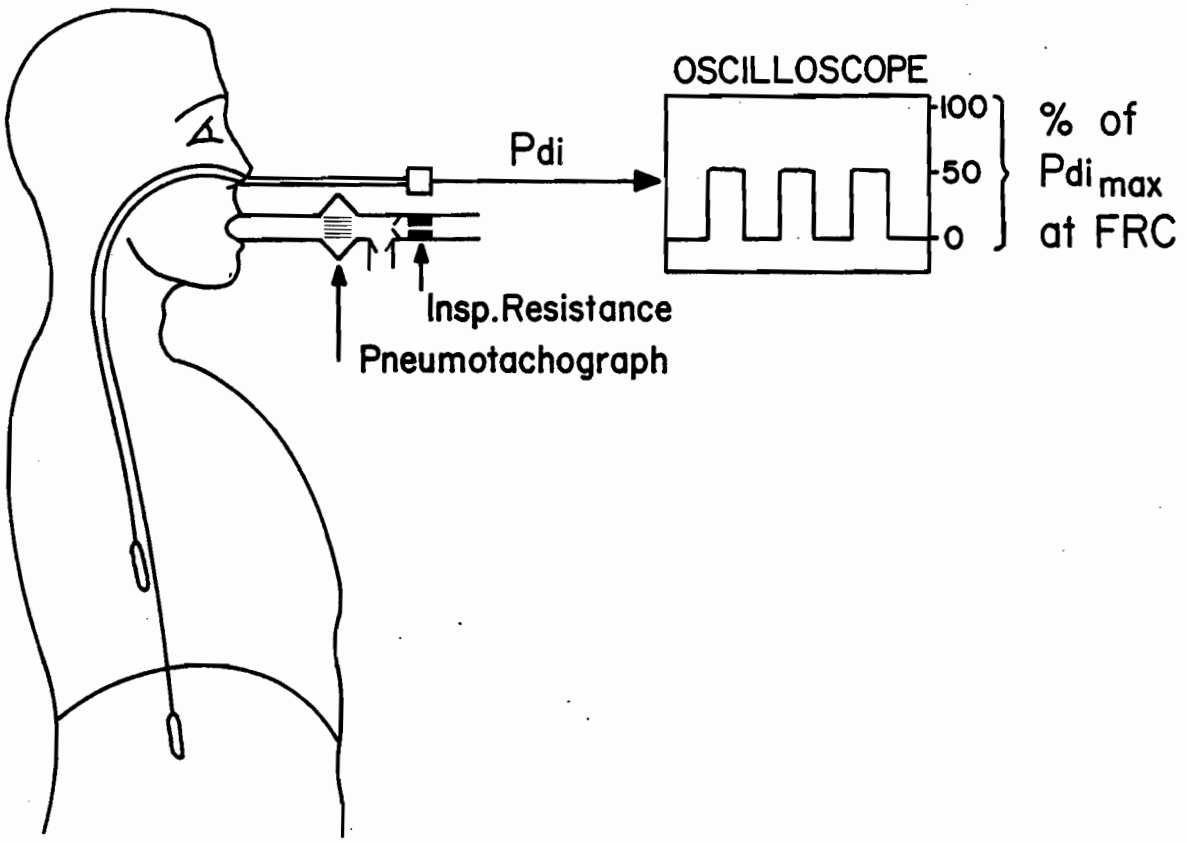

Figure 1: Diagrammatic representation of the experimental design. An inspiratory resistance helped subject breathe at a given predetermined transdiaphragmatic pressure (Pdi). Pdi measured with two balloons was displayed on vertical axis, and tidal volume or time on abscissa of an oscilloscope.

to perform, they did not know either the percentage of Pdi_{max} that they had to achieve with each breath, or the percentage of oxygen that they were inspiring.

d) Results

During the fatigue runs, in every subject the minute ventilation ranged from 10 to 15 l/min and the breathing frequency ranged from 10 to 15 breaths/min. This minute ventilation was chosen by each individual. The end tidal Pco_2 remained constant or slightly increased throughout each run but the increase never exceeded 3-4 torr. Fig. 2 shows tracings obtained during a run with the subject generating about 75% of Pdi_{max} while breathing 13% O_2. The tracings on the left are those obtained at the beginning of the run and those at the right were obtained at the end. They are typical of all runs. At the beginning, Pm, Ppl, Pg, and Pdi were similar during each inspiration. At the end, the swings in Ppl and Pm became greater while the swings in Pg became smaller. The Pdi was not sustained for as long a period during each inspiration and the duration of inspiration was reduced. Eventually a point was reached when the subject became unable to generate the predetermined Pdi. At this point, the ventilatory pattern became irregular and disorganized. There were transient and rapid changes in Pdi and the subjects experienced a "cogwheel" type of breathing in which inspiration was accomplished in steps. Shortly thereafter the subject could not tolerate the procedure and came off the mouthpiece. The duration from the onset of the

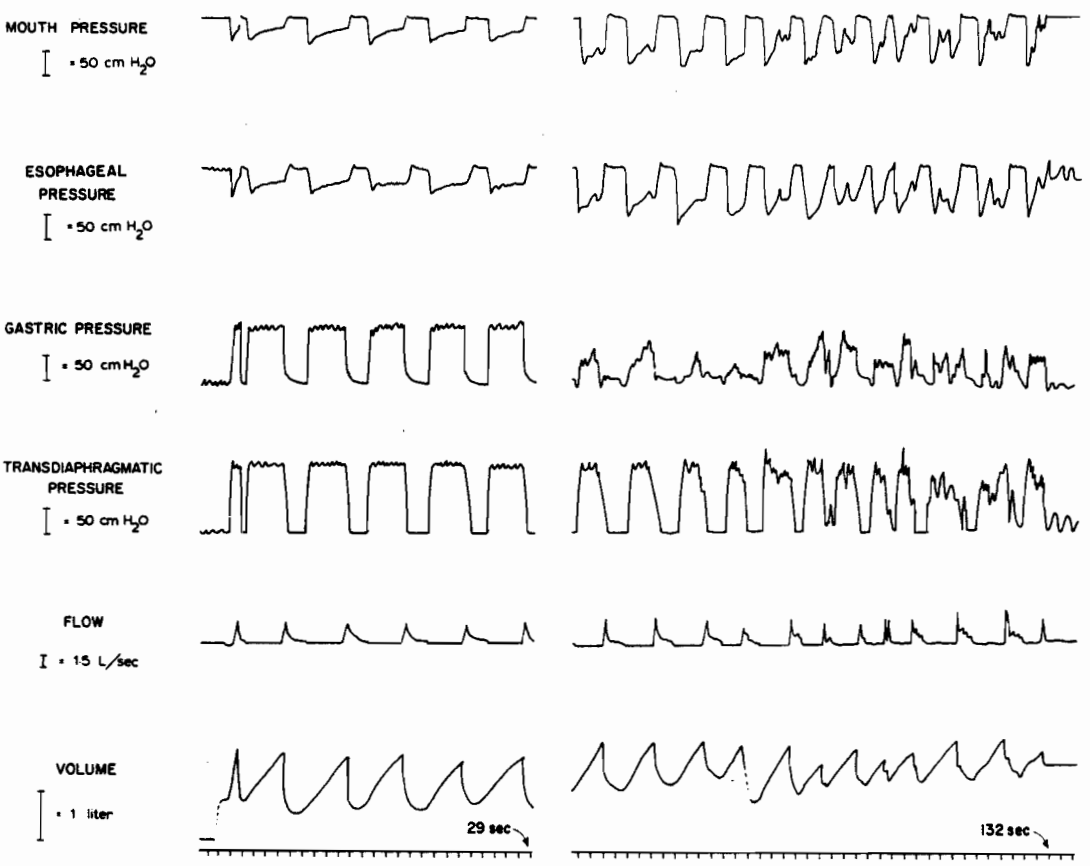

Figure 2: Recorded measurements of an experimental run at 75% of maximum transdiaphragmatic pressure (Pdi_{max}) breathing 13% O_2. Left: first 29 s of performance . Right: last 39 s of the maneuver, which lasted altogether 132 s. Except for Pdi, all pressures were measured relative to atmospheric pressure. Beginning of run (left), all measurements remained similar with each breath. At the end (right), swings in esophageal pressure and mouth pressure increased, while swings in gastric pressure became smaller. Pdi did not reach predetermined value and was not sustained for as long a period with each breath.

run to the point where the subject came off the mouthpiece was designated t_{lim}.

Three interesting sensations were experienced during these runs. In most runs the subjects felt a dull subcostal pain toward the end. One subject frequently developed severe unilateral or bilateral abdominal pain identical to "stitches" experienced during running. Two subjects clearly experienced "second wind" during prolonged runs. They felt that they had almost reached the end point and that they would soon have to come off the mouthpiece. This sensation suddenly disappeared and the subjects were able to continue breathing against the resistive loads generating the appropriate Pdi for considerably longer periods of time. Unfortunately, the subjects did not signal this sensation to the operator so that it was impossible to determine in retrospect if there had been any change in the pressure tracings. Although Pdi remained constant with each breath, it is possible that reciprocal changes in Pg and Ppl occurred, signaling recruitment of other respiratory muscles (see below).

We plotted transdiaphragmatic pressure in percent of maximum Pdi at FRC against t_{lim} (Fig. 3). The relation is curvilinear. The range of Pdi/Pdi_{max} within which the subject performed the maneuvers was 0.4-0.9. Fig. 4 shows a plot of Pdi/Pdi_{max} against the reciprocal of t_{lim}. The resulting curve has an intercept which is the value of Pdi (Pdi_{crit}) that the individual can more or less sustain indefinitely. This was found to be about 40% of the maximum transdiaphragmatic pressure for all three subjects. In the

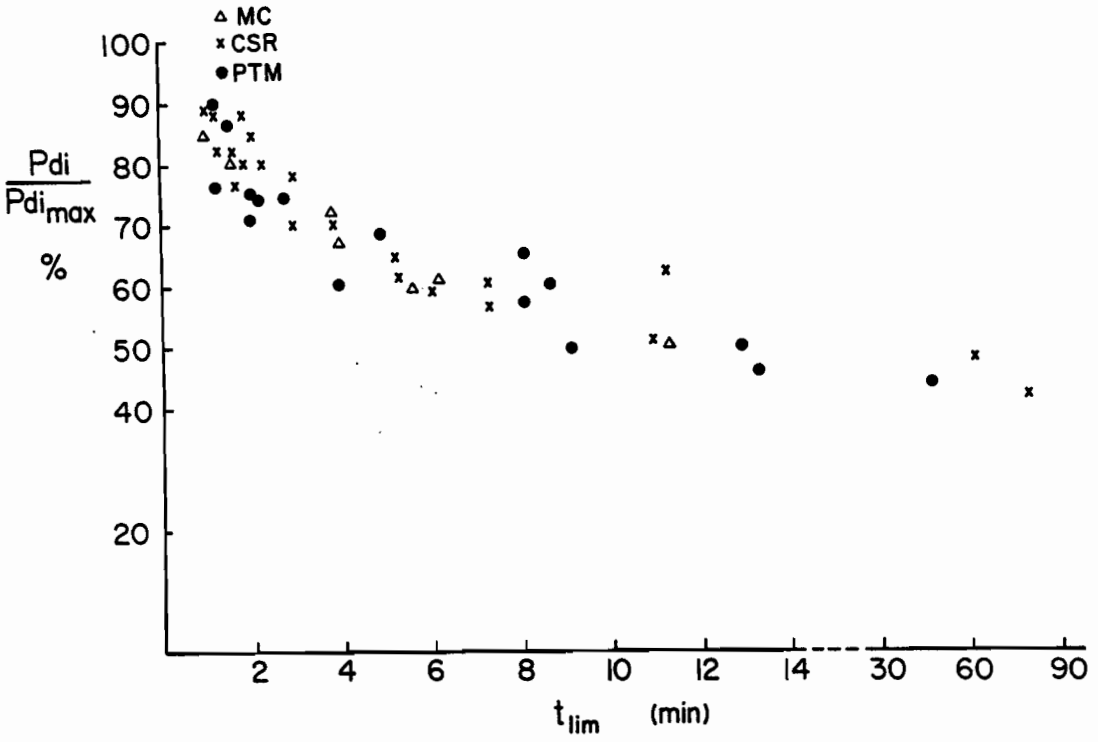

Figure 3: Relationship between transdiaphragmatic pressure (Pdi) expressed as percentage of maximum inspiratory Pdi, (Pdi_{max}) and endurance time (t_{lim}). Each point represents an individual run from each subject. Overall relationship is curvilinear.

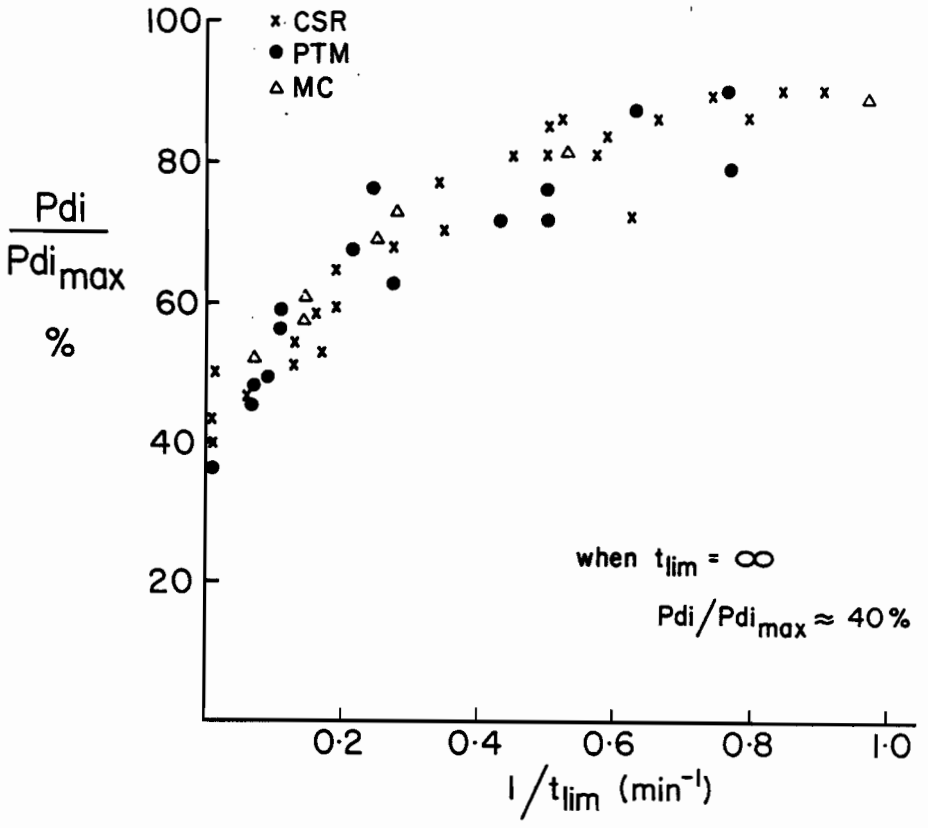

Figure 4: Relationship between Pdi/Pdi_{max} and reciprocal of endurance time ($1/t_{lim}$). Intercept of curve gives approximate value of Pdi (Pdi_{crit}) that the individual can sustain indefinitely.

two subjects who had the same maximum Pdi ($\approx$185 cmH_2O) the Pdi_{crit} was 75 cmH_2O and in the third subject (with a maximum Pdi of $\approx$280 cmH_2O) the Pdi_{crit} was 110 cmH_2O.

A plot of the product of Pdi times total inspiratory time (t_{in}) during each run versus t_{lim} (Fig. 5) reveals a curvilinear relationship. The best-fit line by eye is drawn through the data points. This relationship as discussed below may give insight into the energy consumption of the diaphragm during each run.

The influence of hypoxia on endurance time is shown in Fig. 6 in which the relationship between Pdi/Pdi_{max} and t_{lim} is shown in the two subjects breathing either air or 13% O_2. End-tidal P_{O_2} was approximately 50 torr during the hypoxic runs. The comparison reveals that hypoxia had little if any effect on t_{lim} at high (90%) and low (40%) percentage of the maximum transdiaphragmatic pressure, but had a large effect between these two extremes. Fig. 7 shows the relationship between Pdi/Pdi_{max} and $1/t_{lim}$ during the hypoxic runs. It appears that the intercept Pdi_{crit} is the same as during normoxia. Fig. 8 gives the relationship between the $Pdi \cdot t_{in}$ product and t_{lim} during hypoxia. This is linear and the regression line has a correlation coefficient of 0.99. In contrast, during air breathing the relationship was curvilinear. In both this figure and Fig. 5, data points for $t_{lim} > 15$ mins are not included as they were insufficient to categorize the relationship. In Fig. 9 t_{lim} during air breathing is plotted against t_{lim} during hypoxia at equal values of $Pdi \cdot t_{in}$.

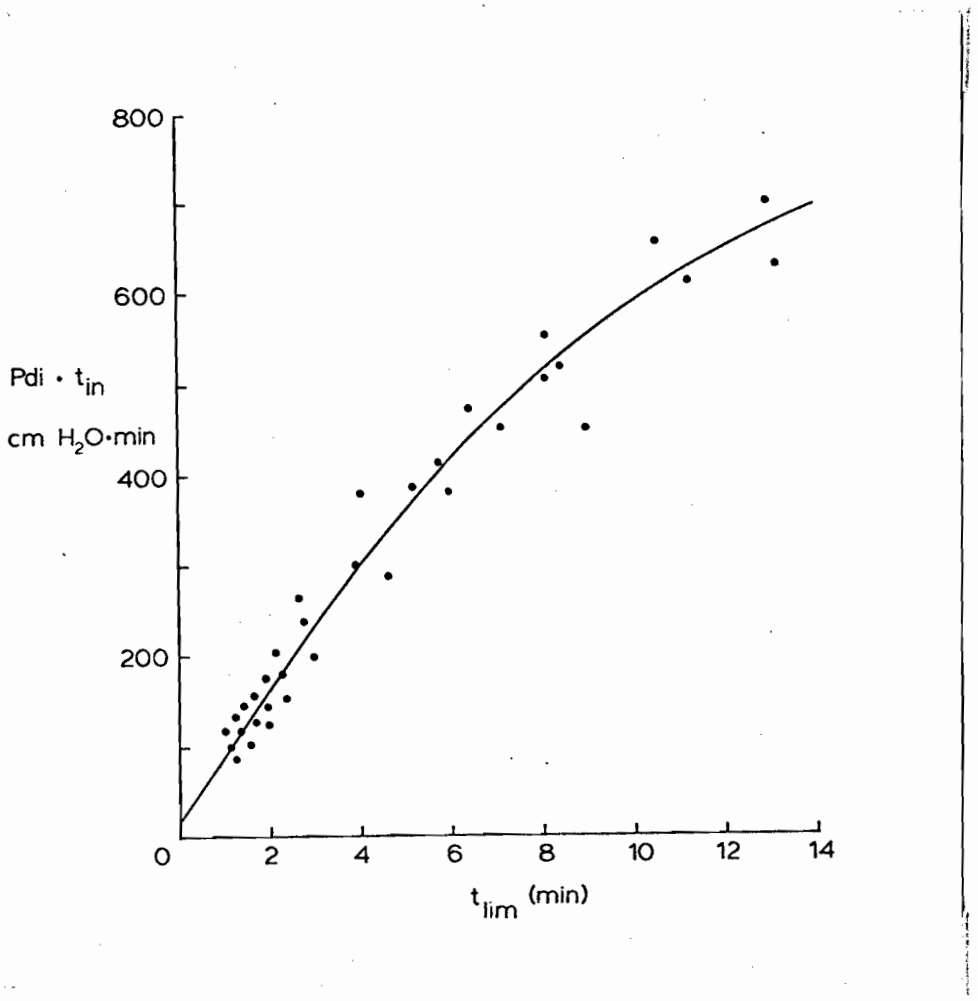

Figure 5: Relationship between product Pdi · t_{in} and t_{lim}. Pooled data from both subjects are shown. Best-fit line by eye is drawn. For further explanation see text.

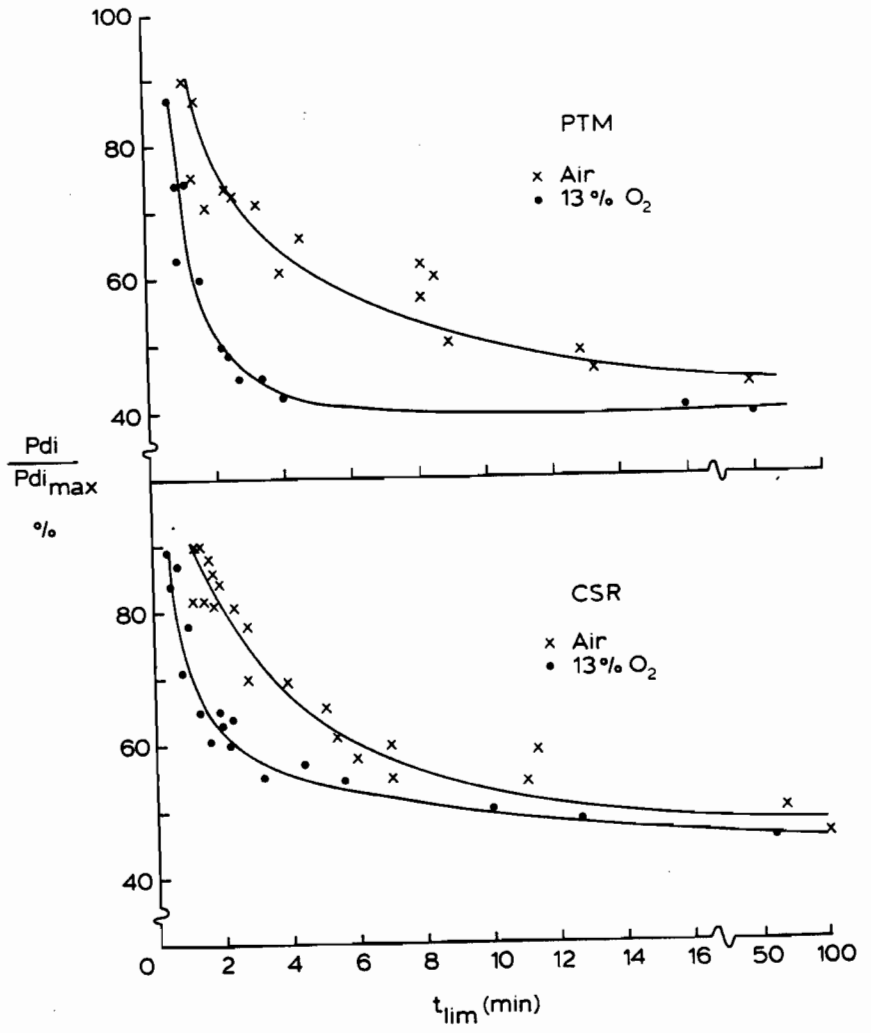

Figure 6: Influence of hypoxia on t_{lim} in two subjects in whom this was measured. Crosses denote the relationship of Pdi/Pdi_{max} with t_{lim} breathing air and closed circles, breathing 13% O_2. The t_{lim} is shorter during hypoxia for any Pdi/Pdi_{max}.

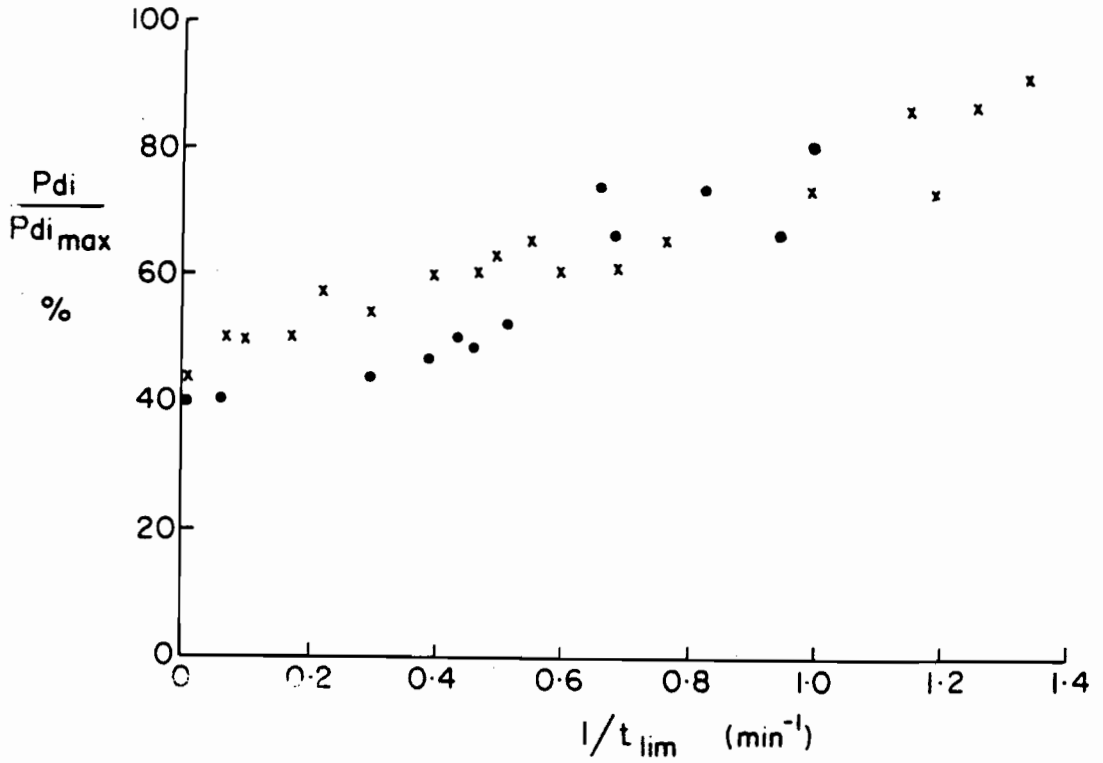

Figure 7: Relationship between Pdi/Pdi_{max} and $1/t_{lim}$ during 13% O_2 breathing . Intercept Pdi_{crit} is not different from that breathing room air (Fig. 4).

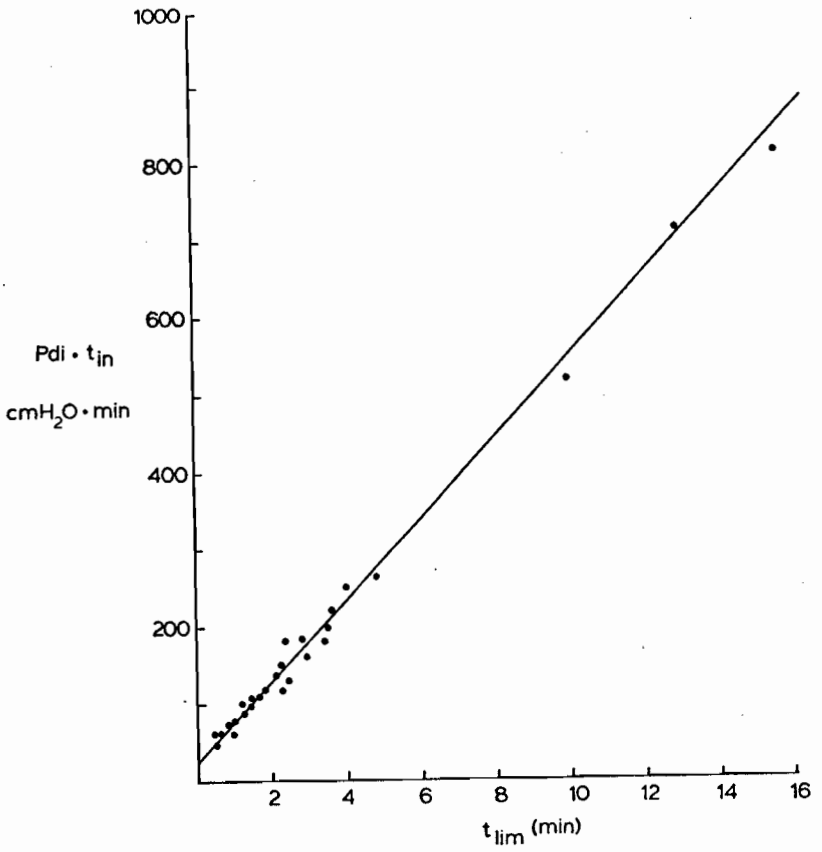

Figure 8: Relationship between the product Pdi · t_{in} and t_{lim} during 13% O_2 breathing. Pooled data from both subjects are shown. Linear regression coefficient is drawn (r= 0.99). For further explanation see text.

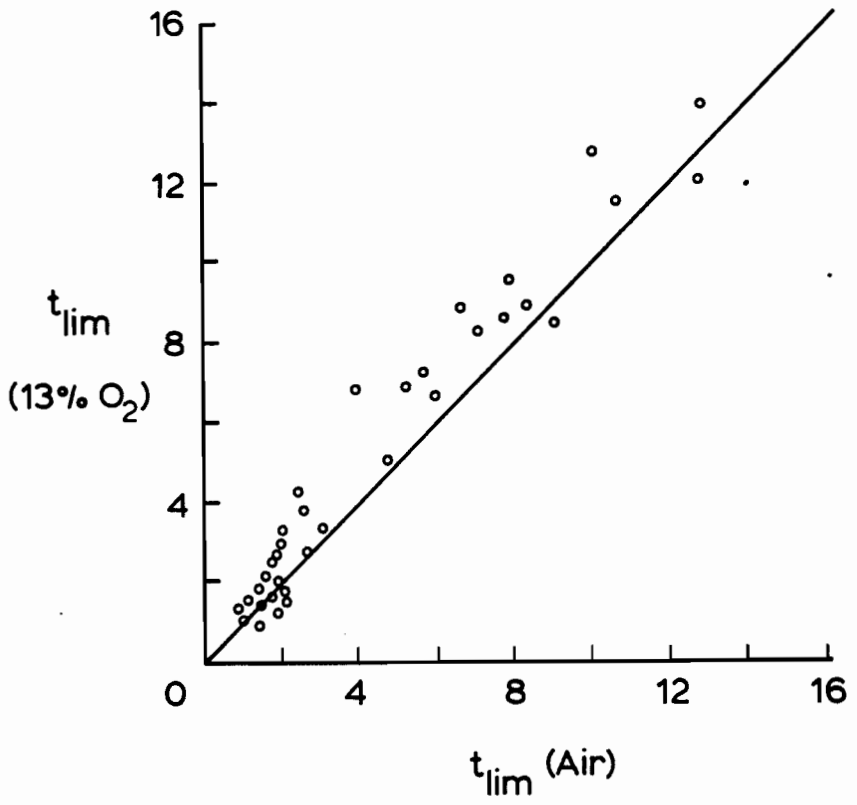

Figure 9: Relationship between t_{lim} breathing air and breathing 13% O_2 at equal values of Pdi · t_{in}. Solid line: line of identity.

In contrast to Fig. 6, t_{lim} during hypoxia was slightly but significantly increased ($P < 0.001$) at equal $Pdi \cdot t_{in}$. The apparent discrepancy between Figs. 6 and 9 is due in part to differences in the ratio t_{in}/t_{lim} between air and hypoxia at a given Pdi/Pdi_{max}. Thus the mean value of t_{in}/t_{lim} in air was 0.501 ± 0.012 (mean $\pm$ 1 SE) and in hypoxia 0.600 ± 0.014 ($P < 0.005$). As a result the ratio $Pdi \cdot t_{in}/t_{lim}$ at equal values of Pdi/Pdi_{max} was substantially greater during hypoxia as shown in Fig. 10.

e) Discussion

Muscle fatigue has been defined as the inability to maintain a predetermined force. Whether or not this is due to motivation, failure of central neurological control, impaired transmission at the motor end plate, accumulation of waste products within the muscle cell, expenditures of energy which exceed supplies or other factors has been and still is the subject of considerable speculation and experimentation. We cannot be certain which of the factors contributed to fatigue in our experiments. We went to considerable length in the present and subsequent experiment to exclude motivation as the cause by introducing competition between subjects and only using subjects who were highly motivated. In other skeletal muscles, Merton (149) has shown that in humans when a muscle diminishes its maximum developed tension while it contracts voluntarily, a tetanic stimulation of the nerve of the muscle does not produce greater tension. Furthermore, he has shown that

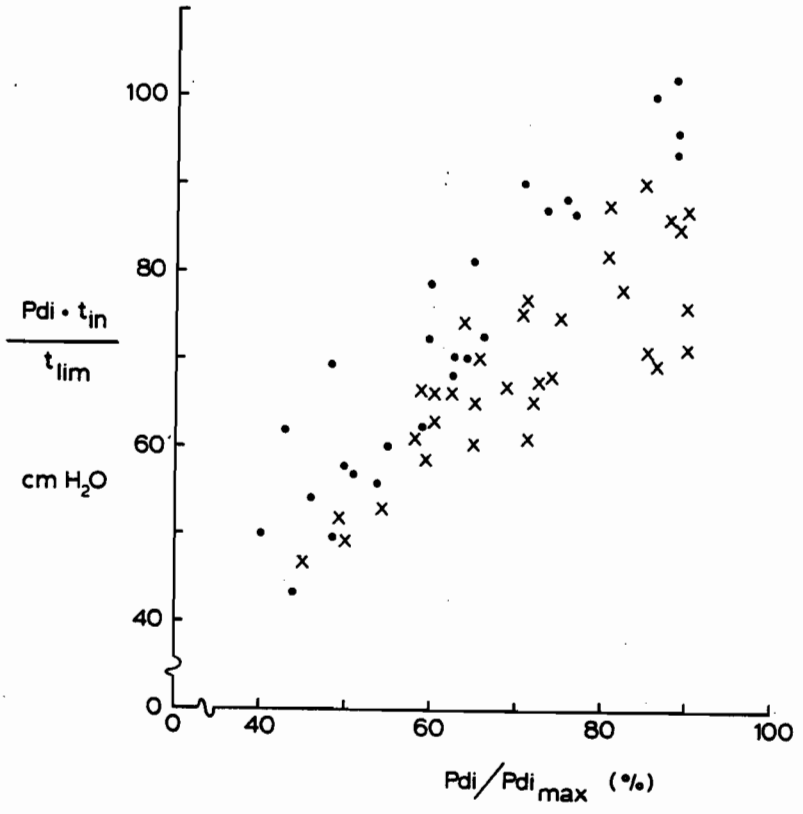

Figure 10: $Pdi \cdot t_{in}/t_{lim}$ during air breathing (X) and 13% O_2 (●) as a function of Pdi/Pdi_{max}. $Pdi \cdot t_{in}/t_{lim}$ in hypoxia for most values of Pdi/Pdi_{max} is greater during hypoxia than normoxia.

during fatigue the action potentials do not diminish in amplitude. Thus, in his experiments the site of fatigue seemed to be primarily in the muscle. Useful predictions about endurance times can be made by assuming that the energy utilization is greater than the energy supply. Since the experiments reported herein were completed, we have measured the electromyogram (EMG) of the intercostal muscles and the diaphragm while breathing with constant Pdi or constant mouth pressure against fatiguing and non-fatiguing loads (230,231). We have shown that there is a shift in the power spectrum of the EMG of these muscles to lower frequencies when they are performing fatiguing work and that this shift occurs long before t_{lim}. Such shift in the power spectrum of the EMG has been correlated with the fatigue of other skeletal muscles (232, 233). No shift was observed during non-fatiguing work. For these reasons we believe that the fatigue we observed in both studies (diaphragmatic fatigue and the subsequent one) is due to physiological changes in the muscles, rather than due to motivation or alterations in central control.

Our results indicate that when the end-tidal level is at FRC and the diaphragm generates a pressure with each breath of about 40% or more of the maximum inspiratory pressure it can generate at FRC,it will eventually become fatigued. It can continue to generate pressures less than about 40% (Pdi_{crit}) of maximum indefinitely. This conclusion would not be justified if the end-expiratory lung volume

varied significantly during the fatigue runs. That this did not occur was demonstrated by the constancy of end-expiratory transpulmonary pressure which did not change during the runs.

Our estimate that the diaphragm can continue to contract at 40% of maximum without becoming fatigued is in general agreement with other data in the literature which suggest that intermittently contracting skeletal muscles can continue to generate tensions of less than 40% of maximum tension without developing fatigue if contraction and relaxation times are approximately equal (234). Furthermore, Lieberman et al (172) found that 40% of the fibers in the guinea pig diaphragm were of the slow-twitch high-oxidative type which, it is hypothesized, do not become fatigued. Thus, they found that during fatiguing stimuli the tension developed by the diaphragm diminished and plateaued at 40% of maximum. The same authors also found that 55% of the fibers in the human diaphragm were of the slow-twitch high-oxidative type. Although, the sampling was obtained from only one site, our results are consistent with their data.

Important questions are 1) whether or not Pdi_{crit} is ever repeatedly exceeded during breathing, and 2) whether respiratory muscle fatigue ever occurs under physiological or pathological conditions. Although our results do not provide an answer to these questions, they establish that the diaphragm can become fatigued in man. In this context we shall now discuss how recruitment of other inspiratory

muscles may influence the development of fatigue and the effect of hypoxia. We then discuss some practical implications of respiratory muscle fatigue both in disease states and exercise physiology.

We have studied fatigue of the diaphragm alone and did so by assigning the diaphragm a particular task to perform with each inspiration. However, in most instances, in which subjects breathe against increased loads, the respiratory muscles do not necessarily generate the same tension with each breath. The muscles may be coordinated in such a way that they are protected against fatigue. In our experiments in which Pdi remained constant during a given run, the components of Pdi (Ppl and Pg) did not remain constant. Toward the end of a run, as illustrated in Fig. 2, the increase in Pg that was prominent at the beginning was small or absent, and therefore the diaphragm was no longer displacing the chest wall (12). Accordingly, more of the pressure developed by the diaphragm was applied to the lung and the swings in Ppl increased in amplitude. These were relatively ineffective in increasing flow and ventilation because of the alinearity of the resistance at the mouth. We interpret these results as indicating that the subject had recruited other inspiratory muscles and that these were sharing the work of breathing with the diaphragm. To prove that recruitment of other inspiratory muscles could influence the onset of fatigue we performed a few runs in which the subject was told to maintain ventilation by any means when he reached the point at which he was unable to generate the

predetermined Pdi. When this occurred the subject was able to maintain ventilation for several minutes, although the Pdi generated with each breath became much less. Thus he tended to relax his diaphragm and to recruit other muscles, delaying the onset of inspiratory muscle fatigue.

A reduction in endurance time as a result of hypoxia might be expected if fatigue results from a failure of metabolic regenerative process in the muscle fiber (224, 149). Lieberman et al (172) related the development of fatigue in the diaphragm to the histochemical characteristics of myofibrillar ATPase and SDH activity suggesting that the rate of ATP depletion was faster than the rate of ATP synthesis. If so, hypoxia might further decrease the rate of ATP synthesis and thereby reduce endurance time. Indeed we found that t_{lim} was diminished by hypoxia when a comparison was made with normoxic conditions at equal values of Pdi/Pdi_{max} (Fig. 6). However, the comparison at equal values of $Pdi \cdot t_{in}$ revealed a small but significant increase in t_{lim} during hypoxia.

To resolve this apparent paradox it is necessary to develop the relationship between energy supplies, energy consumption , and the development of fatigue. Fatigue occurs whenever energy consumption is greater than energy supplies with the result that energy stores are eventually consumed; the demand for energy can no longer be met and the muscle can no longer contract. Monod and Scherrer (225) derived an expression relating the development of muscle fatigue to the total amount of energy consumed as follows:

$$C = \alpha + \beta t_{lim} \quad (1)$$

where C = total amount of energy consumed by the muscle, α = stored energy reserves, and β= rate of energy supplied to the muscle. The mean rate of energy consumption is given by :

$$\dot{C} = (\alpha + \beta t_{lim})/t_{lim} \quad (2)$$

solving for t_{lim}

$$t_{lim} = \frac{\alpha}{\dot{C} - \beta} \quad (3)$$

The value of β depends on a number of variables including O_2 and substrate concentration in arterial blood, muscle flow, and the capacity of muscle cells to utilize energy sources.

The solution of Eq. 1 for t_{lim} yields

$$t_{lim} = \frac{C - \alpha}{\beta} \quad (4)$$

Comparison of the influence of β on t_{lim} from Eqs. 3 and 4 reveals apparently opposite effects. According to Eq. 3, reducing β at a constant $\dot{C}$ reduces t_{lim}. According to Eq. 4, reducing β at a constant C increases t_{lim}. The resolution of this paradox is apparent when it is realized that both t_{lim} and C are variables dependent on β and $\dot{C}$. Thus a reduction of β at a constant $\dot{C}$ will decrease t_{lim} and because $C = \dot{C} \cdot t_{lim}$, total energy consumption must also decrease.

Comparison of the effect of hypoxia on t_{lim} at equal values of C is complicated by these considerations. If under normoxic conditions t_{lim} is different from that

under hypoxic conditions, by definition the rate of energy consumption (C/t_{lim}) must be different. β may be influenced not only by the reduced O_2 content but also by the different value of $\dot{C}$. Thus a better comparison of the effect of hypoxia on t_{lim} is made at equal values of $\dot{C}$.

Our data can be analyzed in terms of $\dot{C}$ and C by using the product $Pdi \cdot t_{in}$ as an index of energy consumption. Because efficiency (E) is the ratio of external work (W) to energy consumption, Eq. 1 can be rewritten as:

$$\frac{W}{E} = \alpha + \beta t_{lim} \qquad (5)$$

The external work performed by the diaphragm with each inspiration is given by $\int Pdi \cdot dVdi$, where Vdi = volume displacement attributable to the diaphragm. Because changes in Pdi were approximately square waves (Fig. 2), so that Pdi remained constant throughout inspiration, the diaphragmatic work during each inspiration simplifies to $Pdi \cdot \Delta Vdi$. The total work performed by the diaphragm (Wdi) during a fatigue run is given by:

$$\begin{aligned} Wdi &= \sum_{i=1}^{i=n} Pdi_i \cdot Vdi_i \\ &= Pdi \sum_{i=1}^{i=n} Vdi \\ &= Pdi(Vdi_1 + Vdi_2 + \ldots + Vdi_n) \\ &= Pdi \cdot Vdi_{tot} \\ &= Pdi \cdot \dot{V}di \cdot t_{in} \end{aligned}$$

where $\dot{V}di$ is the average flow attributable to the diaphragm during the fatigue run and is an expression of the average velocity of contraction, and t_{in} is the total inspiratory time. Substituting in Eq. 5 yields:

$$\frac{Pdi \cdot \dot{V}di \cdot t_{in}}{E} = \alpha + \beta t_{lin} \qquad (6)$$

Although we cannot measure $\dot{V}di$ and E, we have measured $Pdi \cdot t_{in}$ (Figs. 5 and 8). If one assumes that $\dot{V}di/E$ remains constant and substitutes the symbol K for it in Eq. 6, then

$$Pdi \cdot t_{in} = \alpha/K + \beta/K\ t_{lim} \qquad (7)$$

What possible justification is there for assuming that $\dot{V}di/E$ is constant? On the surface, very little. However, for several years circulatory physiologists have used the product of intraventricular pressure and the time over which it developed as a very useful index of myocardial energy requirements (235, 236, 237). This assumes that C is proportional to the product of pressure and time and requires the identical assumption that the ratio of velocity of contraction to efficiency is constant. In spite of the difficulties in justifying this assumption, the tension-time index has proved extremely powerful in the study of myocardial energetics (235,236,237). Furthermore, McGregor and Becklake (238) developed a similar relationship for the respiratory musculature. They found a different relationship between work and oxygen cost of breathing when they compared unloaded hyperventilation to breathing through a resistance. However,

the relationship between force developed by the muscles and their oxygen consumption was the same for the two conditions. They suggested that force might be a useful index of energy consumption and that the discrepant relationship between work and oxygen cost of breathing was due to a reduction in efficiency of the respiratory muscles during resistance breathing.

The calculation of $Pdi \cdot t_{in}$ is similar to the tension-time index. We use this as an index of C. Thus the data in Fig. 9 which are close to the line of identity and which are quite different from the results obtained when t_{lim} is compared at equal Pdi/Pdi_{max} (Fig. 6) represent a comparison at equal values of C and interpretation of these data in terms of a reduction in β due to the reduced O_2 content is difficult as already discussed. The data do indicate, however, that for unknown reasons our subjects spent more time inspiring during hypoxia than they did during normoxia for the same endurance times, so that for the same pressure development the rate of energy consumption was increased. This is shown in Fig. 10 where the ratio $Pdi \cdot t_{in}/t_{lim}$ is used as an index of $\dot{C}$. In contrast when the comparison was made at equal values of C (Fig. 9), t_{lim} was systematically longer during hypoxia ($P < 0.001$) and therefore $\dot{C}$, by definition, was less. Thus the influence of hypoxia analyzed at equal values of Pdi/Pdi_{max} is a comparison made when the rate of energy consumption was greater during hypoxia than breathing air. It is not

surprising that t_{lim} was less during hypoxia. When the analysis was made at an equal value of C, the rate of energy consumption was greater under normoxic condition, and as a result t_{lim} was somewhat longer during hypoxia.

As stated previously, a better way to examine the influence of hypoxia is to make the comparison at equal values of $\dot{C}$. Analyzed this way, we believe our data are consistent with a reduction in β at Pdi greater than Pdi_{crit}. Figs. 5 and 8 are the graphical expressions of Eq. 7 in which α/K is the intercept and β/K is the slope.

For the data obtained during air breathing, the line of best fit was drawn by eye. For the data obtained breathing 13% O_2 a linear regression was calculated by the method of least squares ($r = 0.99$). These lines are superimposed in Fig. 11. We assume that α/K, the Y-intercept, remained constant during runs at different values of $Pdi \cdot t_{in}$. If so, α/K appears to be uninfluenced by hypoxia. For any value of $Pdi \cdot t_{in}$, β/K is given by the slope of the straight line connecting the intercept to that $Pdi \cdot t_{in}$. This graph is similar to one used by Monod and Scherrer (225). β/K remained constant during the hypoxic runs and was therefore independent of $\dot{C}$. This was not the case during normoxia in which β/K was similar to that during hypoxia for longer t_{lim} but increased as t_{lim} decreased and $\dot{C}$ increased. Figure 12 shows how β/K varied as a function of Pdi/Pdi_{max} during air and hypoxia. It appears as if the rate of energy supplied to the diaphragm was maximal during hypoxia even at relatively low values of Pdi/Pdi_{max}, whereas during normoxia

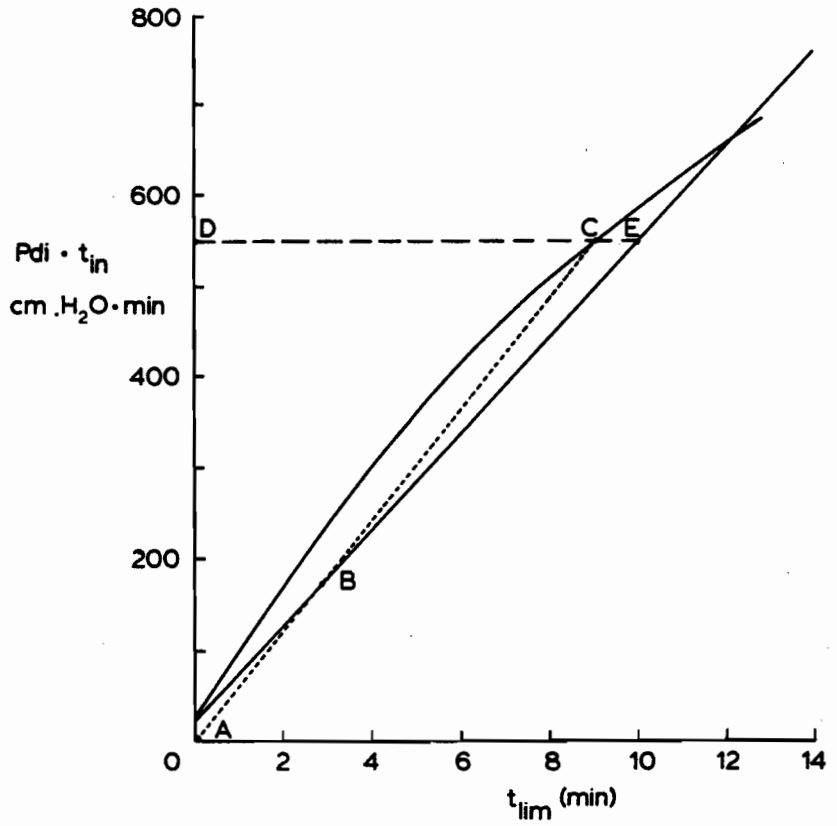

Figure 11: Best-fit line by eye from Fig. 5 superimposed on linear regression line from Fig. 8 (solid lines). See text for further explanation.

the rate of energy supplied was able to increase as Pdi/Pdi_{max} increased.

The slope of a straight line drawn from the origin to any given $Pdi \cdot t_{in}$ has the units of $Pdi \cdot t_{in}/t_{lim}$ which we assume is directly proportional to $\dot{C}$. The dotted line ABC in Fig. 11 is an example. The intercepts B and C give the endurance times for hypoxia and normoxia, respectively, at equal rates of energy consumption. For a given $\dot{C}$, the endurance times are less during hypoxia because of the reduced energy supplies. However, for a given $Pdi \cdot t_{in}$ (as illustrated by the dashed line DCE) t_{lim} is somewhat prolonged for reasons already discussed. Due to the scatter of data in Figs. 5 and 8, the confidence we have in the accuracy of the lines in Fig. 11 is somewhat limited. Therefore this graph should not be interpreted quantitatively. However, we believe that it does illustrate qualitatively the influence of hypoxia and $\dot{C}$ on β and t_{lim}. We conclude that for a given rate of energy consumption hypoxia reduces β and this leads to a reduction in endurance time.

This conclusion is in agreement with the results of Kaijser (208) who studied the influence of hypoxia on small muscle groups and reported that an inspired O_2 content of 10% in helium caused a reduction in endurance time. However, it is at variance with the results published by Tenney and Reese (52) who measured endurance times while breathing at various percentages of maximum breathing capacity in athletes. They found that the influence of breathing 9% O_2 in N_2 was trivial compared to air. Their

comparisons were made at equal minute ventilation so that power development during the two runs was probably equal.

McGregor and Becklake (238) found that respiratory muscle efficiency was diminished during resistance breathing compared to hyperventilation at the same power. This could result in some inspiratory muscles contracting isometrically during resistance breathing compared to hyperventilation. If so, during resistive loading both the velocity of contraction and efficiency may be reduced compared to hyperventilation at the same power. If the ratio between the two ($\dot{V}/E$) remained constant, this would have no influence on $\dot{C}$. On the other hand if the reduction in E was greater than $\dot{V}$, $\dot{C}$ would increase during resistive loading at the same external power. From Eq. 3, t_{lim} would decrease unless β increased to the extent that $(\dot{C} - \beta)$ remained constant. The results presented in Fig. 12 suggest that, in the presence of hypoxia, β was fixed and could not increase as $\dot{C}$ increased. One might predict therefore that hypoxia would have a greater effect on endurance time during resistive loading than during voluntary hyperventilation. Further evidence that this may be so is found in the results of Eldridge (239) who showed that during moderate hyperventilation in room air or 15% inspired oxygen,blood lactate did not increase. Breathing against resistive loads did not cause the blood lactate to rise either. However, breathing hypoxic mixtures against resistive loads did lead to an increase in blood lactate. By inference,the respiratory muscles may depend very little, if at all, on anaerobic

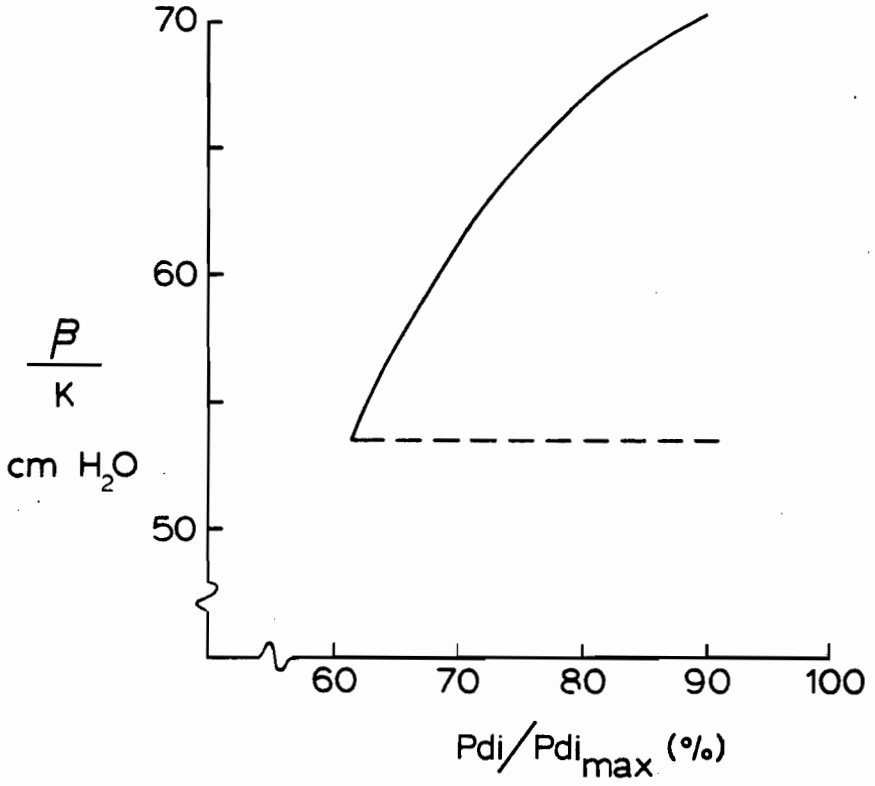

Figure 12: Index of energy supplies to diaphragm (β/K) as function of Pdi/Pdi_{max} during normoxia (solid line) and hypoxia (dashed line). For further explanation, see text.

metabolism with normal lung resistance and compliance even during hypoxia, whereas during high resistive loads under sufficiently hypoxic conditions the supply of oxygen to the respiratory muscles may be inadequate and may lead to anaerobic metabolism to meet the work demand. This could account for the difference between our results and those of Tenney and Reese (52).

A similar explanation might account for our finding that hypoxia had little effect on Pdi_{crit}, whereas at greater resistive loads its effect was apparent. Alternatively if one interprets Figs. 11 and 12 in terms of β alone, hypoxia had no influence on β at t_{lim} greater than 12 mins or Pdi/Pdi_{max} less than 60%. Perhaps there was increased diaphragmatic blood flow induced by hypoxia which by increasing substrate supplies compensated for the diminished O_2 delivery (240). Compensation may also have been accomplished by increasing O_2 extraction.

To summarize, the differences we observed in t_{lim} during normoxia and hypoxia at equal Pdi/Pdi_{max} are attributable, in part, to differences in t_{in}. In addition, it appears that hypoxia reduced the rate of energy supplies when breathing against high loads so that t_{lim} was diminished for any given rate of energy consumption. However, for any given value of total energy consumption, t_{lim} was somewhat prolonged during hypoxia because the rate of energy consumption was decreased more than the rate of energy supplies.

Our observation that β/K continues to increase during normoxia once Pdi_{crit} is exceeded (Fig. 12) is differ-

ent from similar measurements on skeletal muscle in which the relationship between the power output of the muscle and t_{lim} is linear (225). Thus for skeletal muscles, β is constant at its maximal value once the critical power is exceeded. This may not be the case for the diaphragm. Robertson et al (241) found that diaphragmatic blood flow increased exponentially as the work of breathing increased. There was no tendency for perfusion to plateau at a maximal level even at very high work rates. If this is also true for man, diaphragmatic fatigue may have a somewhat different basis than fatigue in the skeletal muscles. In the other muscles, fatigue results when energy supplies reach a maximal value but energy consumption continues to increase. In the diaphragm, fatigue appears to result whenever the consumption of energy is greater than the supply at a particular value of diaphragmatic power. At a greater power, the energy supply appears to increase, but not as much as the energy consumption. As a result, the endurance time is greater than it would be if the energy supplies had remained constant.

Our results do not answer the question whether diaphragmatic fatigue ever occurs under pathological or physiological circumstances. If it does occur, the events following the development of diaphragmatic fatigue when ventilation must continue against an added load remain speculative. Almost certainly the event must be disastrous, although whether or not it leads rapidly to death or whether ventilation is reset at a lower but new steady state which the muscles can manage is unknown.

Respiratory muscle fatigue may also play a role in the sensation of dyspnea and may lead to exercise limitation. Predictably, if fatigue does play a role in the pathogenesis of respiratory failure and in exercise limitation the report by Leith and Bradley (55) that the respiratory muscles can be trained to increase static strength and endurance may have exceedingly important therapeutic practical implications.

III. 2. 2) Fatigue of the Inspiratory Muscles and their Synergic Behavior

a) Summary

The time (t_{lim}) required to produce inspiratory muscle fatigue was measured in five normal subjects breathing at FRC against a variety of high inspiratory resistive loads. In every breathing test the subjects generated with each inspiration a mouth pressure which was a predetermined fraction of maximum Pm (Pm_{max}). They continued breathing until they were unable to generate this Pm. The Pm/Pm_{max} that could be generated indefinitely (Pm_{crit}) was around 60%. The inspiratory power output at that level of breathing was 6.6 kgm/min ($\dot{W}_{crit}$). In three of those subjects the same experiment was conducted at an end-expiratory volume of FRC + ½ inspiratory capacity (IC). The higher lung volume was actively maintained by the subjects watching end-expiratory transpulmonary pressure on an oscilloscope. For any fraction of the maximum mouth pressure at FRC + ½ IC (Pm_{max}), t_{lim} was shorter than at FRC. Pm_{crit} decreased to 30% Pm_{max} and $\dot{W}_{crit}$ to 2.6 kgm/min. Monitoring the abdominal pressure (Pg), revealed that the contribution of the diaphragm and intercostal accessory muscles alternated in time, possibly postponing the onset of fatigue.

b) Introduction

In the previous experiment, we have described fatigue of the diaphragm in man. However, recruitment of other

inspiratory muscles while breathing against resistive loads may play an important role in protecting the respiratory system against the development of fatigue. Accordingly, in this study we have examined the response of all the inspiratory muscles to breathing against inspiratory resistive and fatiguing loads.

This study has two major aims: 1) to determine at FRC and at a higher lung volume, the critical level of alveolar pressure and power output of the inspiratory muscles which is just sufficient to produce fatigue; 2) to examine qualitatively the interaction of the diaphragm and intercostal/accessory muscles when breathing against fatiguing inspiratory resistive loads.

c) Methods

Five normal laboratory volunteers were studied in a seated position breathing through an inspiratory resistive load at FRC. Three of these were also studied while voluntarily maintaining an increased end-expiratory lung volume of FRC plus ½ inspiratory capacity, (IC).

1) Measurements at FRC: Prior to each fatigue experiment, the subject performed a maximum inspiratory effort for 2-3 seconds at FRC with the airway totally obstructed. This maneuver was repeated 4 to 5 times, with an interval of 3 - 5 minutes between trials, in order to obtain the maximum inspiratory pressure (Pm_{max}) that the subject could generate at FRC. Pm_{max} was highly reproducible within

individuals, varying by 4 to 5 cmH_2O from day to day. All individuals had a Pm_{max} between -130 and -145 cmH_2O. After measuring Pm_{max}, the subjects breathed through a Hans-Rudolf valve (Fig. 1), the inspiratory inlet of which was connected to a Starling resistor consisting of a collapsible latex tube in an airtight plexiglass chamber. While breathing through the tube, the pressure in the chamber was adjusted to limit inspiratory flow rate at a maximum of 0.5 - 0.7 l/s. Expiration was not loaded. In this system, inspiratory flow rate was independent of mouth pressure and the inspiratory resistance was directly proportional to the magnitude of the mouth pressure swings. The subject was instructed to generate a mouth pressure (Pm) with each inspiration which was a predetermined fraction of Pm_{max}. Pm was displayed to the subject on an oscilloscope and was maintained constant throughout inspiration and with each breathe, until the subject could no longer develop it. No instructions were given to the subject regarding how he was to develop the target Pm. Thus, he was free to use his diaphragm or his intercostal/accessory muscles or both in order to develop Pm. At the end of the run when the subject could no longer produce the required Pm by any means, we assume that all of the inspiratory muscles, not just the diaphragm were fatigued. The subject was unaware of the magnitude of the Pm that he had to generate. This was achieved by using the zero suppression so that the magnitude of the pressure swing was not displayed to the subject. The subject chose his own tidal volume and frequency. The endurance time (t_{lim}) was the time from the

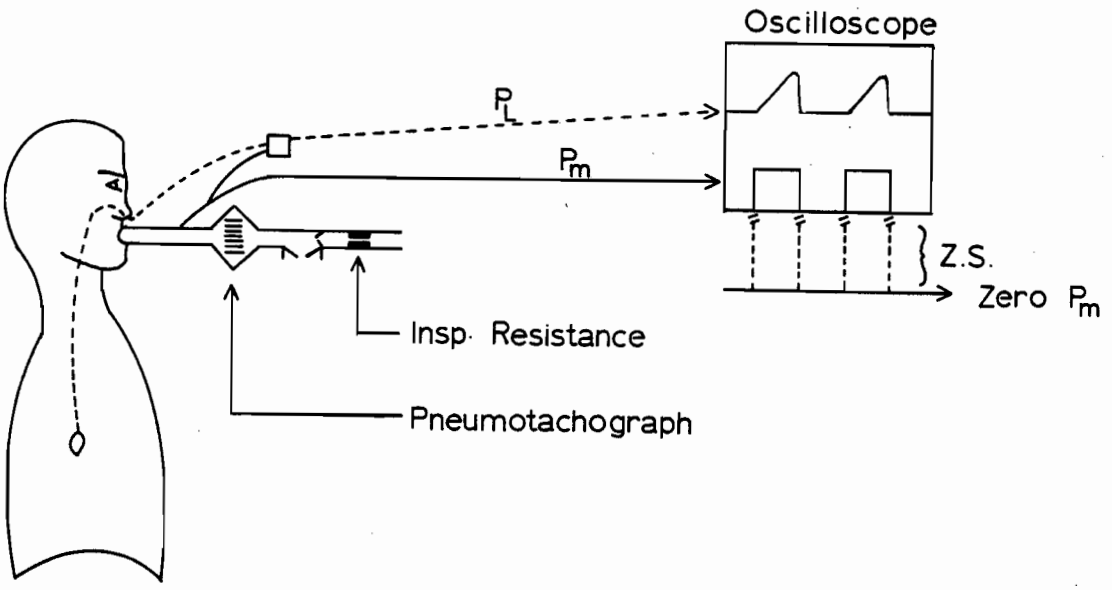

Figure 1: Diagrammatic representation of the experimental design. An inspiratory resistance helped the subject breathe at a given predetermined mouth pressure (Pm). Pm was displayed on the vertical axis and time on the abscissa of an oscilloscope. Transpulmonary pressure (P_L) was measured by an esophageal balloon and was displayed on the upper part of the oscilloscope. (For further details see text).

beginning of the run until the subject could no longer tolerate the procedure and came off the mouthpiece. This occurred two to three breaths after he was unable to achieve and sustain the predetermined target Pm.

Esophageal pressure, (Pes), mouth pressure, flow, volume and end tidal CO_2 and O_2 were measured as in the experiment III. 2. 1. (Methods).

During 4 or 5 fatigue runs at different levels of mouth pressure in all subjects, we also measured transdiaphragmatic pressure (Pdi), gastric pressure (Pg) (as described in Chapter III. 2. 1. Methods), and the motion of rib cage and abdomen (Fig. 2). The motion of the rib cage and abdomen were measured by two pairs of magnetometers. (See Chapter II. 2. 2. Methods).

2) Measurements at FRC plus ½ Inspiratory Capacity: The whole experimental procedure in three subjects was repeated at a higher end-expiratory lung volume; namely, FRC plus ½ inspiratory capacity. This volume was maintained voluntarily without external assistance. Constancy of the end-expiratory volume was achieved by displaying transpulmonary pressure (P_L) on the oscilloscope. Thus, during inspiration the subjects watched the Pm display as earlier described in order to achieve the target pressure whereas during expiration, they observed P_L and kept it constant at end expiration and equal to the static transpulmonary pressure at FRC plus ½ inspiratory capacity. A run was not accepted if end-expiratory transpulmonary pressure did not remain constant with ± 1 cmH_2O

throughout the whole run. Unfortunately, we were unsuccessful in studying the influence of hyperinflation produced by positive pressure breathing at the same lung volume. The pressure required to produce this degree of hyperinflation caused fatigue of the lips so that a tight mouthpiece seal could not be maintained.

All signals in each run were recorded on an 8 channel Hewlett-Packard strip chart recorder.

The order in which the experiments were done was randomized in each subject. Each subject performed 1, and occasionally two fatigue runs per week. Since the endurance time may be influenced by subjective factors, we chose subjects who were highly motivated to improve motivation and cooperation; competition between individuals was introduced and encouraged.

d) Results

The minute ventilation during all fatigue runs ranged between 8-13 liters per minute and respiratory frequency between 10-14 breaths per minute. Each subject was free to choose his own minute ventilation and respiratory frequency. End-tidal P_{CO_2} remained constant throughout the run, except for the last few breaths when it increased slightly. The increase was never greater than 3-4 mmHg.

In most runs the subjects felt a dull pain in the area of the neck and shoulders, parasternally and subcostally. All subjects experienced "dyspnea" during trials in which fatigue resulted, while no dyspnea was reported during non-

fatiguing runs. All subjects experienced "second-wind" during prolonged runs. They felt that they had almost reached their limit of tolerance and that they would soon have to terminate the run. This sensation suddenly disappeared and the subjects were able to continue breathing against the resistive loads generating the target Pm for considerably longer periods of time.

Fig. 2 shows a tracing taken during a whole single run with the subject generating Pm of approximately 75% of Pm_{max} at FRC. These tracings are representative of all runs in all subjects both at FRC and the higher lung volume. Although Pm and transpulmonary pressure swings remained constant throughout the whole breathing test, there were marked fluctuations in Pdi and Pg. At the beginning of Fig. 2 Pg was positive during each inspiration and Pdi was large (A). This was followed by a period of several breaths when the inspiratory fluctuations in Pg were virtually negligible and Pdi became smaller (B), with transient increases in Pg in early expiration. Subsequently the inspiratory Pg swings increased once more and became so positive that they went off scale (C). Here Pdi was also maximal. Finally, towards the end of the run, Pg became negative during a part or all of inspiration and Pdi became minimal (D). The corresponding changes in the A-P diameter of the abdomen show that an increase in Pg was accompanied by an increase in A-P diameter of the abdomen. When Pg remained unchanged the A-P diameter also did not change, while, when Pg decreased during inspiration, the A-P diameter also decreased. Although there is no

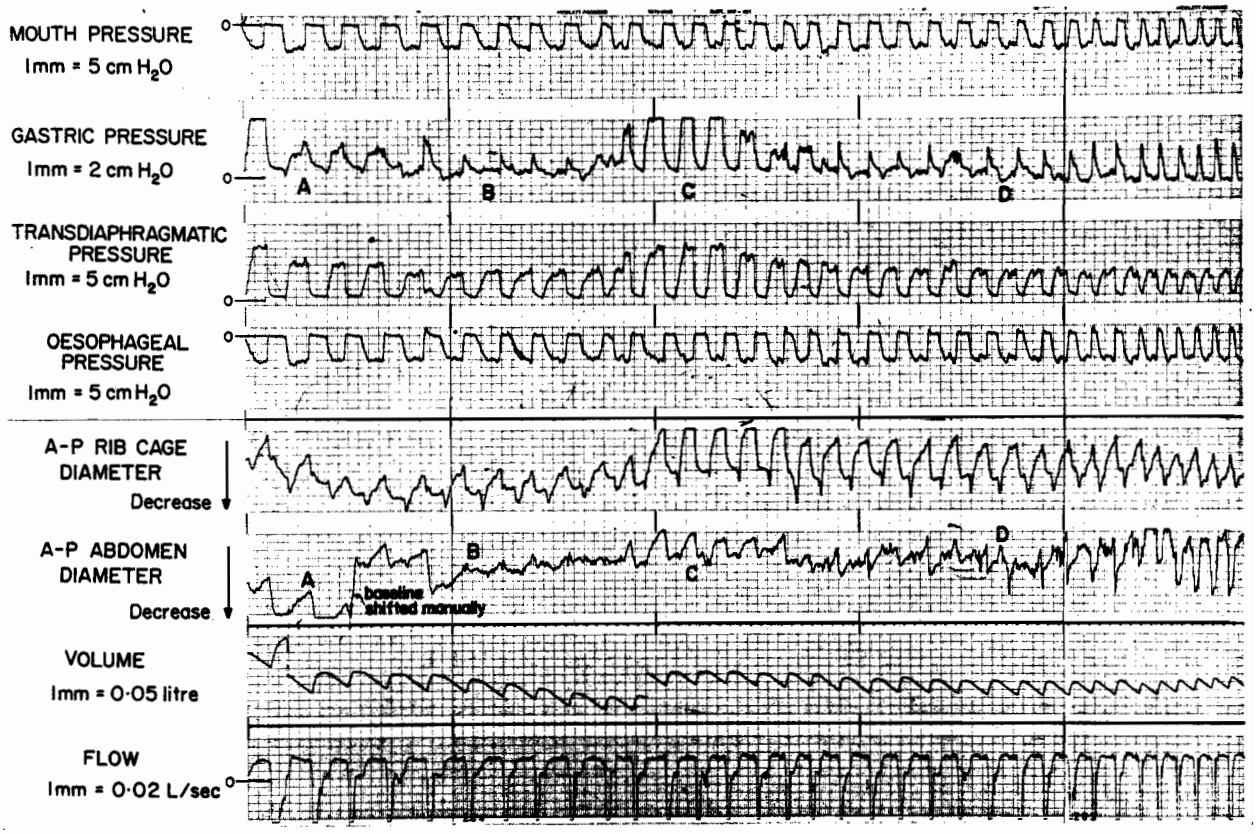

Figure 2: Recorded measurements of an experimental run at 75% of maximum mouth pressure (Pm_{max}). Except for transdiaphragmatic pressures (Pdi), all pressures were measured relative to atmospheric pressure. The swings in mouth pressure and esophageal pressure remained constant throughout the run while those in gastric pressure (Pg) and Pdi varied. Increase in Pg during the inspiration was associated with an increase of the anteroposterior (A-P) diameter of the abdomen (A, C); when Pg did not change the A-P diameter of the abdomen did not change either (B); when Pg decreased the A-P diameter also decreased (D).

clear cut separation of the various types of breaths, the subjects spent approximately 1/3 of the time breathing with high Pg, 1/3 with constant Pg and the remaining third with negative Pg. The difference between the maximum and minimum inspiratory Pdi observed in a given run ranged from 35-100 cmH_2O. It was neither constant in all runs in the same subjects, nor among the subjects.

We plotted Pm as percent of Pm_{max} at FRC against t_{lim}. A representative example is shown in Fig. 3A. Pm varied from 40 to 90% of Pm_{max}. The relationship between Pm/Pm_{max} and t_{lim} is curvilinear and appears to reach an asymptotic value of Pm/Pm_{max} at about 50%. This asymptotic value of Pm/Pm_{max} is better visualized in Fig. 3B, where the abscissa is the reciprocal of t_{lim}. The resulting curve has an intercept on the ordinate which is the value of $Pm(Pm_{crit})$ when t_{lim} is equal to infinity. This is the value of Pm that the individual can more or less sustain indefinitely. In Fig. 4, the best-fit line drawn by eye is displayed for all subjects plotted in the same manner as Fig. 3B. The intercepts indicate that Pm_{crit} ranges from 50 to 70% of Pm_{max} or a mean value of -80 cmH_2O. To assess the significance of the relationship between t_{lim} and Pm/Pm_{max}, an exponential curve was fitted through the data points of each subject yielding correlation coefficients of 0.75, 0.891, 0.802, 0.987 and 0.882 with a p value < 0.01 in each case.

A representative example of the results obtained in one subject at FRC and at the higher lung volume plus $\frac{1}{2}$

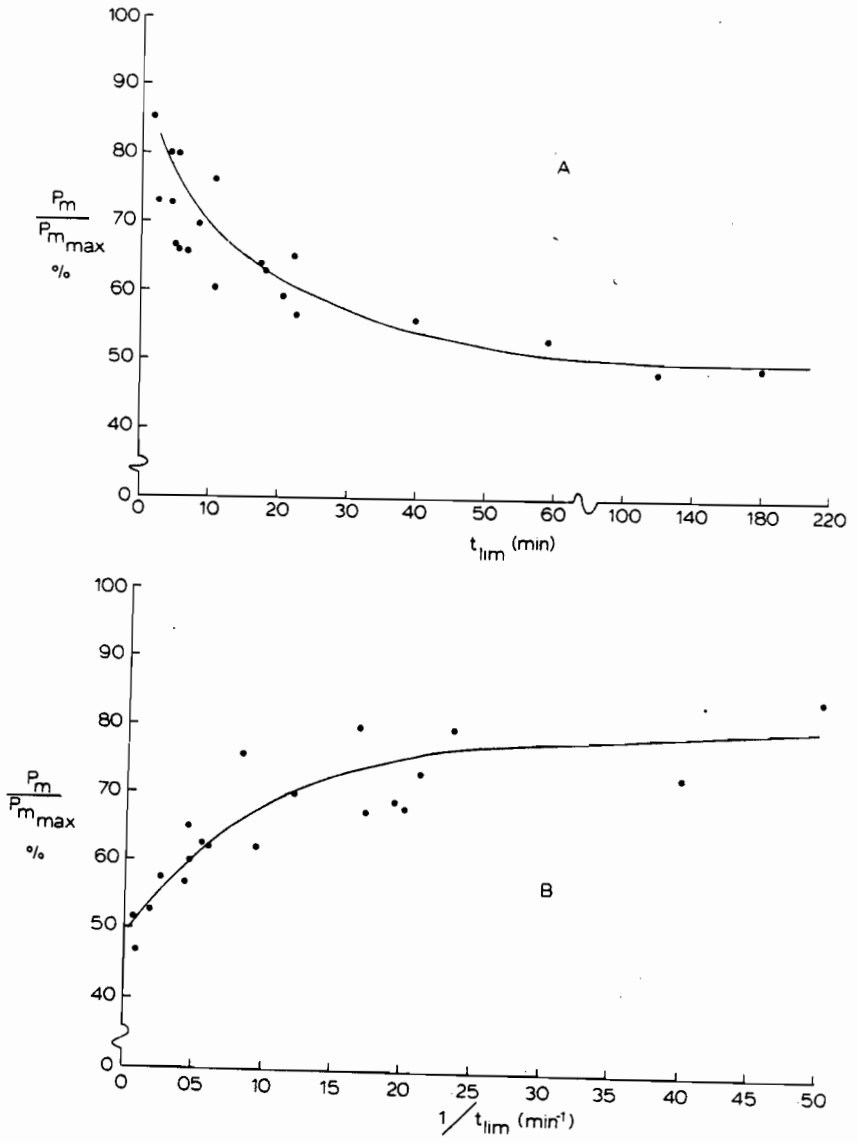

Figure 3: Mouth pressure (Pm) as percentage of maximum inspiratory pressure (Pm_{max}) plotted as a function of endurance time (t_{lim}) in the upper panel (A) and against the reciprocal of endurance time ($1/t_{lim}$) in the lower panel (B). Each point represents an individual run in one subject. The intercept of the best-fit curve drawn by eye through the data points in panel (B) gives the approximate value of Pm that the individual can sustain indefinitely (Pm_{crit}).

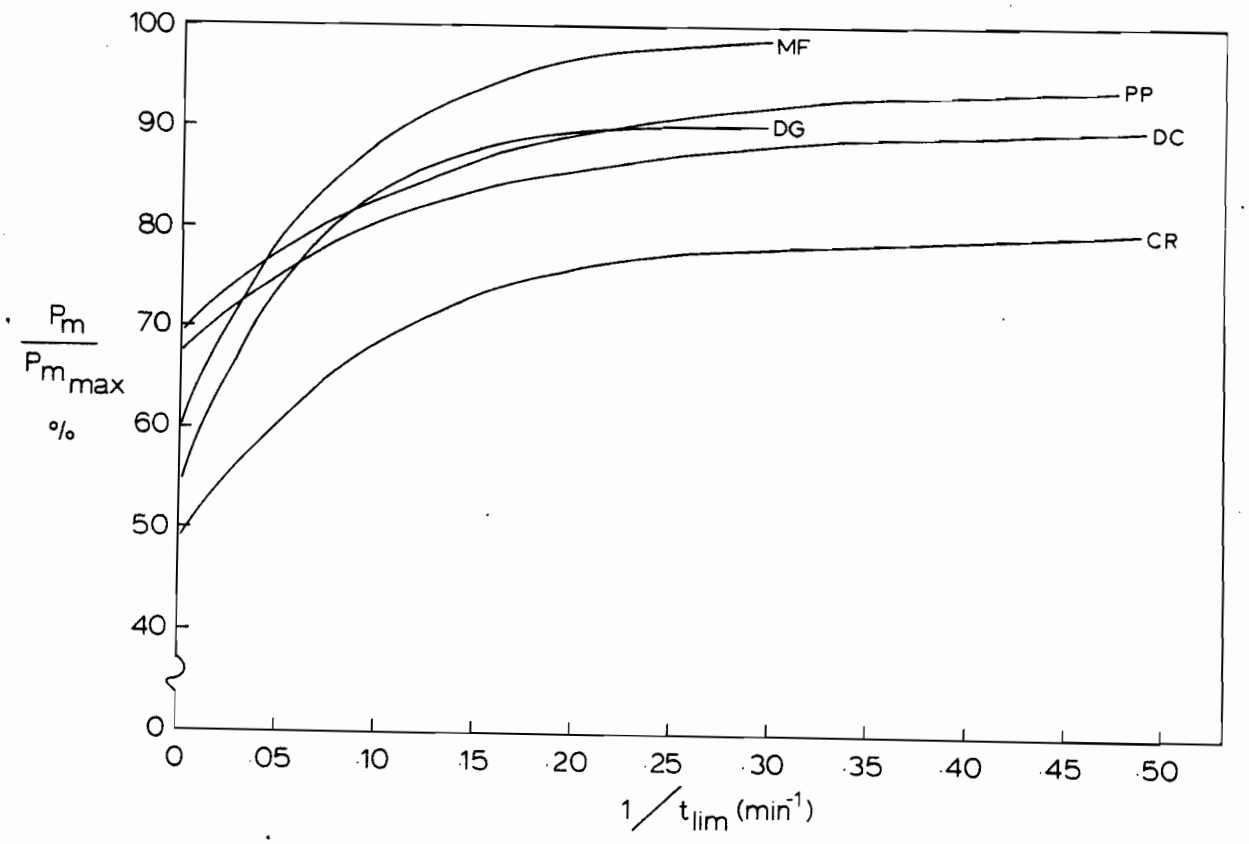

Figure 4: Relationship between Pm/Pm_{max} and the reciprocal of endurance time ($1/t_{lim}$) in all subjects. Each curve represents the line of best-fit drawn by eye through the data points of each subject (See Fig. 3B). The intercept of each curve gives the approximate value of Pm that each individual can sustain indefinitely (Pm/Pm_{max}).

inspiratory capacity is shown in Fig. 5 in which the absolute value of Pm is displayed on the left ordinate and Pm/Pm_{max} on the right. These are plotted against t_{lim}. The values obtained at FRC are shown by the closed circles and at FRC plus ½ inspiratory capacity by the x's. In Fig. 6, the best-fit curve drawn by eye for the relationship between Pm/Pm_{max} versus $1/t_{lim}$ at FRC and FRC+ ½ IC are shown for all three subjects. The correlation coefficient of the exponential curves fitted through the data of each subject had values of 0.907,0.805, and 0.960 ($p < .01$ in all cases). At the higher lung volume, Pm_{crit} was substantially less than it was at FRC. Furthermore, the t_{lim} for any Pm/Pm_{max} was shorter.

Because Pm remained essentially constant during each inspiration and from breath-to-breath during a given fatigue run, the critical power ($\dot{W}_{crit}$) of the respiratory system in each individual was obtained by multiplying the Pm_{crit} by the minute ventilation during the particular run. At FRC this value ranged from 6.0 to 7.2 kilogram meters per minute (mean 6.6 kgm/min). It should be noted that this value of $\dot{W}_{crit}$ is not the total critical power of the inspiratory muscles but represents the power over and above that required for ordinary tidal breathing in order to ventilate against a resistive load. Furthermore, it neglects any power required to distort the chest wall. In Fig.7, the effect of hyperinflation on Pm_{crit} and $\dot{W}_{crit}$ is shown in all three subjects. The mean Pm_{crit} and $\dot{W}_{crit}$ fell from their values at FRC, to -27 cmH_2O and 2.4 kgm per minute, respectively.

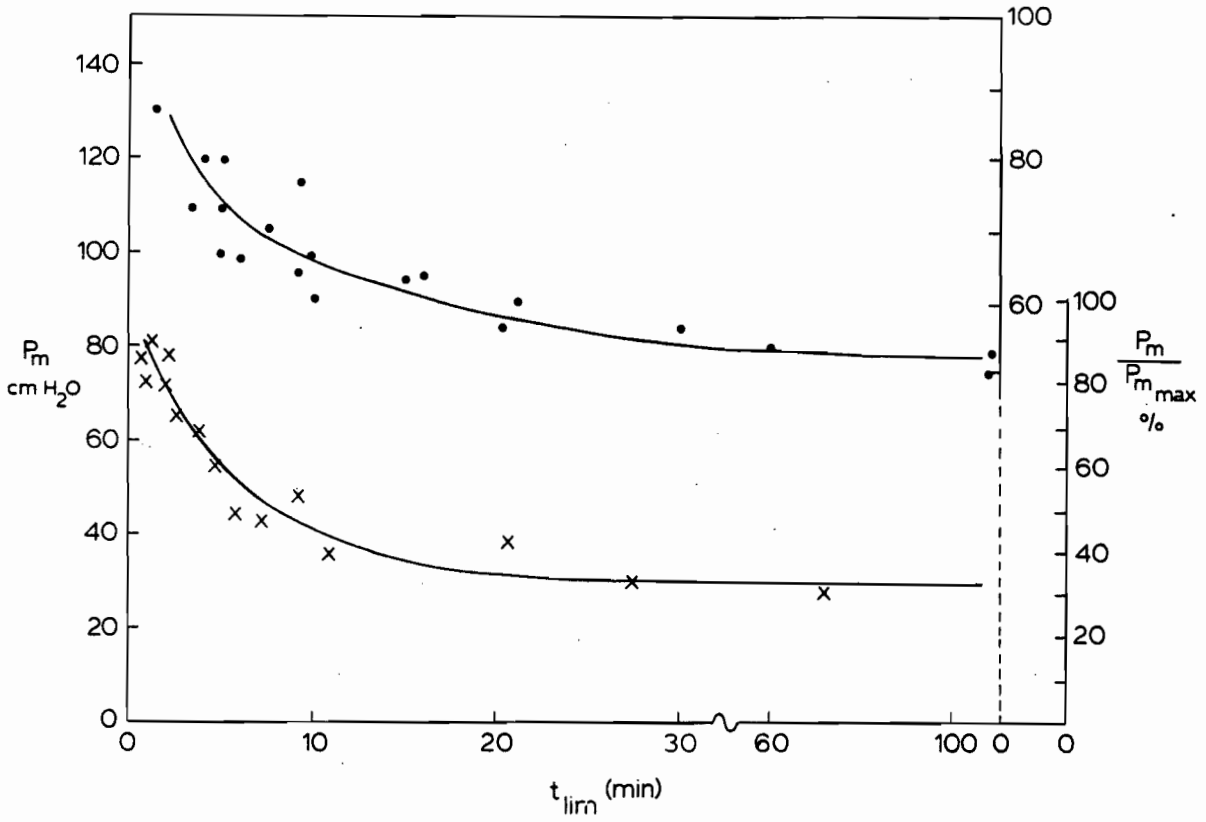

Figure 5: Effect of lung volume on endurance time (t_{lim}) in minutes. Left ordinate - mouth pressure (Pm). Right upper ordinate - mouth pressure as percent of maximum (Pm/Pm_{max}) at FRC (solid circles). Right lower ordinate - Pm/Pm_{max} at FRC + ½ inspiratory capacity (crosses). Note the difference in the asymptotic value of Pm/Pm_{max} at the two lung volumes.

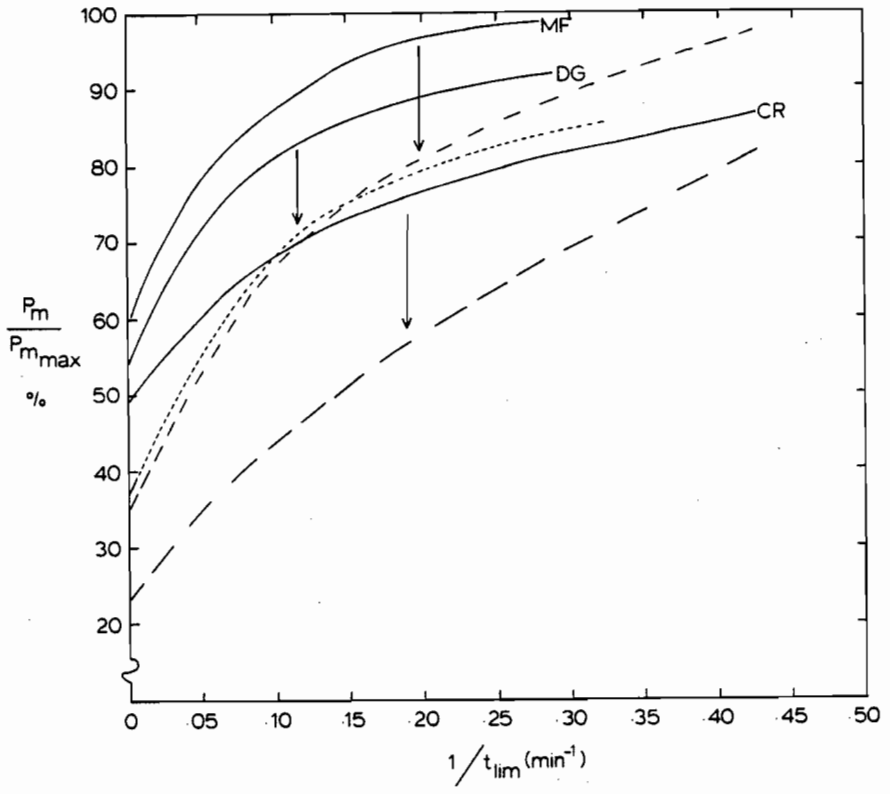

Figure 6: Relationship between Pm/Pm_{max} and the reciprocal of endurance time ($1/t_{lim}$) in three subjects at FRC (solid lines) and FRC + ½ IC (interrupted lines). In each subject the intercept (Pm_{crit}) decreased at higher lung volume. The arrows indicate in each subject the change in relationship of Pm/Pm_{max} against $1/t_{lim}$ from FRC to FRC + ½ IC

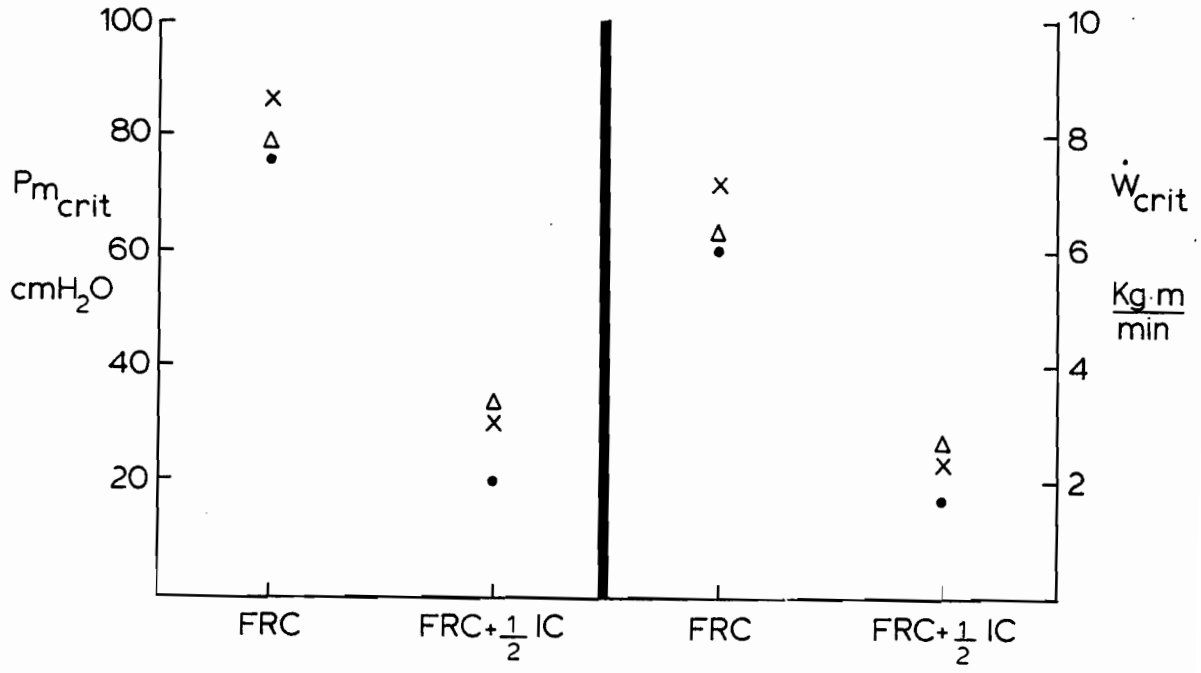

Figure 7: Comparison of critical mouth pressure (Pm_{crit}), left panel, or critical power output ($\dot{W}_{crit}$), right panel, at FRC and FRC + ½ IC. The higher lung volume substantially decreased both Pm_{crit} and $\dot{W}_{crit}$.

e) Discussion

Our data in this study indicate that fatigue of the respiratory muscles can be experimentally produced in humans. Therefore, it potentially exists in patients and may possibly be a cause of respiratory failure. The data also indicate that the vulnerability of the inspiratory muscles to develop fatigue is greater at higher lung volumes and that the contribution of different inspiratory muscle groups to the respiratory pressure swings varies during a given fatigue run.

The variation in Pdi and Pg shown in Fig. 2, while Pm and esophageal pressure (Pes) remained constant, reveals variation in the strength of diaphragmatic contraction during a given fatigue run. We interpret this as indicating recruitment and derecruitment of other respiratory muscles. An increase in abdominal pressure during inspiration greater than that which occurs during an inspiration in which the diaphragm is the only muscle contracting, signals recruitment of the abdominal muscles whereas smaller abdominal pressure swings signal recruitment of intercostal/accessory muscles of inspiration (25). A fall in abdominal pressure during inspiration below the value during relaxation at FRC indicates strong recruitment of intercostal/accessory muscles.

Although we do not believe the data in Fig. 2, can be quantified in terms of the pressure contributed by the intercostal/accessory muscles, because the abdominal muscles were presumably not relaxed (25), we can make qualitative

statements about recruitment of these muscles. During the period B when the abdominal pressure did not change from its value at resting end-expiration, the intercostal muscles were recruited. This relieved the diaphragm of performing the task of increasing abdominal pressure in order to displace the chest wall (12). During the period C when abdominal pressures went off-scale, the abdominal muscles were probably recruited placing the diaphragm at a better mechanical advantage so that more transdiaphragmatic pressure was developed for a given electrical activation of the diaphragm (22). During period D when Pdi was minimal, abdominal pressure fell below its resting end-expiratory value indicating strong recruitment of intercostal/accessory muscles of inspiration. The increases in gastric pressure during expiration signals recruitment of expiratory muscles. If this were to lower the end-expiratory volume below FRC, relaxation of the expiratory muscles would produce a transient fall in abdominal pressure to a value less than that of resting FRC. This does not explain our data because during period D, gastric pressure remained below that at resting FRC throughout almost all of inspiration. Furthermore, expiratory muscle recruitment did not lower FRC because there were no systematic changes in end-expiratory transpulmonary pressure during the runs.

The abdominal and rib cage A-P diameter changes in Figure 2 must be interpreted cautiously. Certainly the efforts far-exceeded the limits established by Konno and Mead (136) in which the rib cage and abdomen behave as

compartments with a single degree of freedom. Furthermore, as the subject approached the limit of his endurance, his whole body moved as he fought to attain the target Pm. Thus, deformation and motion artefacts obscure the significance of these tracings.

Whether or not the variation in contributions of the diaphragm, intercostal/accessory muscles of inspiration, and abdominal muscles to the work of breathing during the development of inspiratory muscle fatigue protects against the development of fatigue and prolongs endurance time is unknown. However, during periods of smaller Pdi, the diaphragm may recover from fatigue to a certain extent whereas during periods when there are large positive abdominal pressure swings, the intercostal/accessory muscles are relatively relaxed and may also undergo some recovery. This might well postpone the eventual development of inspiratory muscle fatigue.

In the experiments performed at FRC plus ½ inspiratory capacity, it is necessary to emphasize that no positive end-expiratory pressure was used to assist the subjects in maintaining their hyperinflated state. Thus, the hyperinflation was achieved by a contraction of the inspiratory muscles throughout the whole respiratory cycle. We estimate from their relaxation pressure-volume curves that the pressure developed by the inspiratory muscles to maintain this lung volume was in the order of 15 cmH_2O. The fact that the inspiratory muscles never relaxed throughout the respiratory

cycle may explain the change in Pm_{crit} expressed as percentage of Pm_{max} that was observed with hyperinflation. This situation is different from hyperinflation produced by positive end-expiratory pressure for at least two reasons: First of all, because the inspiratory muscles remain contracted during expiration, the rate of energy consumption will be increased and secondly, because the sustained contraction of the inspired muscles may reduce the perfusion and thus the rate of energy supplied to the muscles. However, one would predict that hyperinflation produced by any means would result in a reduction in endurance times and critical inspiratory power because the length-tension relationships of the inspiratory muscles results in a decrease in the maximum pressures these muscles can develop as lung volume increases. In addition, flattening of the diaphragm with increases in lung volume should decrease the pressure generated by the diaphragm for any given value of diaphragmatic tension.

It is unfortunate that we were unable to compare positive pressure breathing with voluntary hyperinflation. However, in terms of making predictions about the development of fatigue in patients with airways obstruction and hyperinflation, it may surprisingly turn out that voluntary hyperinflation is more appropriate. Asthmatics with severe airway obstruction and hyperinflation do not breathe out with esophageal pressures that are markedly positive (242). Furthermore Martin, Engel and myself (unpublished observations) have found that during expiratory resistance breathing, leading to hyperinflation in normal subjects, the amount of negative inspira-

tory work performed during expiration is substantially increased.

Thus the influence of hyperinflation on the development of inspiratory muscle fatigue may have considerable clinical significance. We speculate on this in Fig. 8 in which the maximum pressure-volume diagram of the respiratory system is presented. The dashed line joins the two critical values of alveolar pressure we found at FRC and FRC + ½ inspiratory capacity. Two hypothetical dynamic pressure volume loops are also drawn for a subject with airway obstruction (such as during an acute asthmatic attack). In the absence of hyperinflation, the dynamic alveolar pressures generated with each inspiration do not attain the critical values. With hyperinflation, however, the dynamic pressures generated for a given degree of obstruction may exceed the critical values and result in fatigue. Thus, although hyperinflation in the face of airways obstruction may improve the distribution of inspired gas and of gas exchange by opening up or distending the narrowed airways, it places the inspiratory muscles at a mechanical disadvantage and may well predispose to the development of fatigue. Sharp et al (243) measured maximum inspiratory mouth pressures in patients with chronic airways obstruction and calculated theoretical values based upon the patients' lung volumes and the normal volumes of Rahn et al (218). The measured values were minus 15-60 cmH_2O (mean -30 cmH_2O), whereas the calculated values ranged from zero to -64 cmH_2O (mean -30 cmH_2O). Our studies indicate that

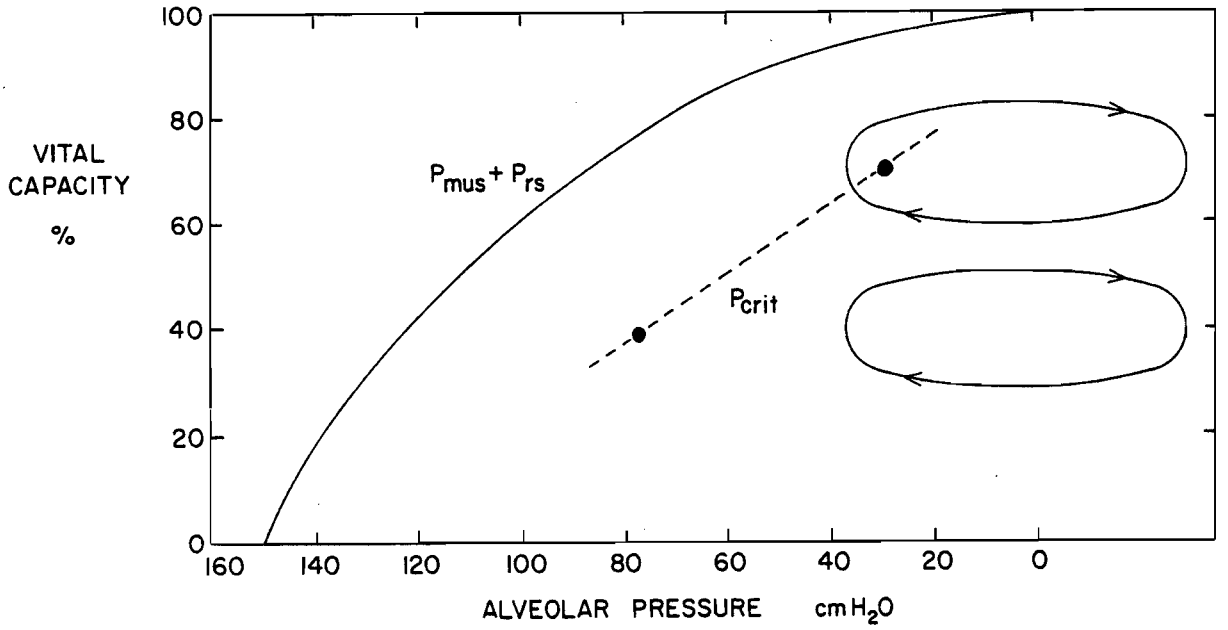

Figure 8: Maximum inspiratory pressure-volume diagram. The maximum inspiratory pressure of the respiratory system at different lung volumes is given by the solid curve ($P_{mus} + P_{rs}$). The dashed line joins the two critical values (P_{crit}) measured at FRC and FRC + ½ IC. At these two lung volumes, two hypothetical dynamic alveolar pressure-volume loops are also drawn. At FRC, the dynamic alveolar pressures do not attain P_{crit} while at FRC + ½ IC, P_{crit} is exceeded.

at normal FRC, the critical pressure of the inspiratory muscles is between 50 and 70% of maximum. Combining the two estimates indicates that the critical inspiratory alveolar pressure swings in airway obstruction would be in the order of -20 cmH_2O. If hyperinflation is maintained by a sustained contraction of the inspiratory muscles throughout expiration, as was the case in our hyperinflation experiments, the critical pressure would fall to about -10 cmH_2O. These values are very likely to be exceeded in such patients particularly during asthmatic attacks and exercise.

Although the exact biochemical basis of fatigue remains unknown, Kugelberg and Edstrom (224) have shown that in muscle preparations in situ in which single motor units were electrically stimulated at frequencies within the physiological range, fatigue was mainly due to a failure of metabolic regenerative processes to rebuild depleted substrates in the fibers. Burke et al (157) used intracellular micropipettes to stimulate individual motor units in cat gastrocnemius and they identified individual motor units in which fibers did not fatigue, others that fatigued slowly and still others that fatigued rapidly. The fatiguability of these motor units was correlated with the type of muscle fibers, the speed of contraction and the oxidative capacity of fibers in the motor unit. Consistent with this observation are the findings of Lieberman et al (172), who found that the percentage of maximum tension maintained after 30 min of stimulation of isolated guinea pig diaphragm correlates

with the percentage of high-oxidative slow-twitch fibers which, it is hypothesized, do not become fatigued. Although the phenomenon of fatigue in terms of metabolic processes in the muscle seems to be more complex (Chapter III. 1), as a first approximation, a muscle undergoing a task of exhaustion can be considered as a system where the equation of energy as proposed by Monod and Scherrer (225) can be applied:

$$\frac{W}{E} = \alpha + \beta t_{lim} \qquad (1)$$

or

$$\dot{W} = \frac{\alpha E}{t_{lim}} + \beta E \qquad (2)$$

where W is the total work performed at a time t_{lim}; E is the efficiency of the muscle, α is the energy stored within the muscle, β the rate of energy supplied to the muscle and $\dot{W}$ the rate of work output of the muscle.

Although explanations of fatigue in terms of energetics may not be strictly speaking correct, they lead to useful predictions that can be tested. For example, Eq. 2 implies that when t_{lim} approaches infinity; $\dot{W}_{crit}$ depends directly on the rate of energy supplied to the muscle and the efficiency. For a given β, E can vary thus influencing $\dot{W}_{crit}$. This may explain a discrepancy between the data of Tenney and Reese (52) and our own.

Our estimate of a critical inspiratory power at FRC of 6.6 kgm meters per minute or approximately 13.5

calories is substantially smaller than the critical power found by Tenney and Reese (52) during voluntary isocapnic hyperventilation. From their data, the $\dot{W}_{crit}$ seems to be in the order of 100 calories. Although our values represent only the "added" inspiratory power while the results of Tenney and Reese (52) represent inspiratory and expiratory power, the difference is so large that we feel that it cannot be explained by differences in the method of calculating power. McGregor and Becklake (238) found that for the same amount of external work, the oxygen cost of breathing through a resistance was substantially greater than that during isocapnic hyperventilation. This suggests that the efficiency was reduced in our experiments compared to the experiments of Tenney and Reese (52). Such a decrease in inspiratory muscle efficiency may very well account for the difference between our results and theirs. In addition our results may explain, in part, the change in efficiency reported by McGregor and Becklake (238).

With intercostal/accessory muscle recruitment, the diaphragm contracts at least, in part, as a fixator. When abdominal pressure swings are negative during inspiration it may even contract pliometrically (25). Inspiratory abdominal muscle recruitment may also be substantially greater during resistive breathing. Thus, the diaphragm and abdominal muscles would require substantial oxygen consumption with little contribution to positive external work. Furthermore, while breathing against resistive loads the distortion of

the chest wall may be significant and thus the inspiratory muscles consume energy without performing external work that is measured by traditional pressure-volume diagrams. During hyperventilation the respiratory muscles may work in such a way that a greater percentage of the developed pressures are producing external work with less distortion.

If inspiratory muscle fatigue results when the rate of energy consumption exceeds the rate of energy supply, it is possible to summarize the important physiological factors which will have a major influence on the development of fatigue. The rate of energy consumption is determined in large part by the tension the muscle develops relative to maximum tension it is capable of developing. The importance of maximum tension is illustrated by the hyperinflation experiments which reduced Pm_{max} and markedly facilitated the development of fatigue. Thus, conditions which increase the work of breathing and/or decrease the strength of the inspiratory muscles, predispose to the development of fatigue by increasing energy consumption. On the other hand, a reduction in blood flow or in O_2 and substrate content of arterial blood will reduce energy supplies. This alone or accompanied by a reduction of energy stores (a function of nutritional state) and/or the efficiency by which these energy sources are converted to external work (a function of the load) will also predispose to fatigue.

These five factors, strength, load, energy supplies, energy stores and efficiency, should be taken into consideration in trying to predict respiratory muscle fatigue. Any

or all of them may be adversely affected by a variety of diseases. It is likely, although not yet proven, that respiratory muscle fatigue and subsequent respiratory failure is the result.

CHAPTER IV

CONCLUSIONS

Πρός γάρ τό τελευταῖον ἐκβάν
ἕκαστον τῶν πρίν ὑπαρξάντων κρίνεται.

Δημοσθένης

All facts are judged according
to the final results.

Demosthenes.

It is shown in this thesis that the voluntary use of the muscles involved in respiration can alter the topographical distribution of regional lung volume and distribution of inspired gas and by inference, the topography of pleural pressure. It is shown also, that the inspiratory muscles become fatigued by breathing against resistive loads. The protocol of this study is original in that, for the first time, it is shown that the ventilation distribution is altered by selective use of the respiratory muscles. Furthermore, the fatigue of respiratory muscles for the first time is specifically examined as a potential cause of respiratory failure. The above epigrammatical claim can be further analyzed in the following conclusions, each of which represents an original contribution to the field of respirology.

1) The vertical distribution of regional lung volume was assessed by ^{133}Xe technique in four subjects in the lateral decubitus posture at 20, 40, 60 and 80% of vital capacity, under high and low diaphragmatic tone. When the transdiaphragmatic pressure (Pdi) was low, i.e., diaphragm was 'relaxed', the vertical gradient of alveolar expansion was greater than when the Pdi was high. At 70% of total lung capacity (TLC), this difference expressed as percent of regional TLC (TLC_r) decreased from 19.7 ± 1.7 (mean ± 1 SE) % TLC_r when the Pdi was low to 3.9 ± 1.5 % TLC_r when the Pdi was high.

2) Under both conditions (high Pdi or low Pdi) the gradient of alveolar expansion tended to be curvilinear with a discontinuity at the level of the mediastinum.

3) The expired ^{133}Xe concentration versus volume in lateral decubitus posture showed that the slope of the expired plateau was steeper when inspiration of ^{133}Xe was performed with the diaphragm relaxed than under conditions when the diaphragm was voluntarily contracted.

4) In six subjects in lateral decubitus position the washout of a bolus of helium (inhaled from residual volume) during a relaxed slow expiration showed that the Phase IV started at 58 ± 1.6% vital capacity, while when Pdi exceeded 30 cmH_2O, Phase IV commenced at 8.2 ± 0.8% VC.

5) Closure of airways in the dependent regions does not appear to account for the high Phase IV in the lateral decubitus position when the diaphragm is relaxed.

6) In supine posture expiration with high Pdi resulted in a flatter slope of the alveolar plateau and smaller closing volume by 3.7 ± 0.4 % VC.

7) Contraction of the diaphragm increased the amplitude of cardiogenic oscillations during the helium washout. This may result from a facilitation of transmission of the cardiac impulse to the lung by a stretched mediastinum.

8) The distribution of inhaled gas from functional residual capacity was substantially affected by selective use of the respiratory muscles. In upright, supine and lateral postures the tracer gas (either ^{133}Xe or He) could be distributed preferentially to dependent lung regions by an 'abdominal' inspiration, whereas an 'intercostal' inspiration resulted in a more even distribution or one preferential-

ly to the nondependent zones.

9) When the tracer gas was inhaled at residual volume, differences in distribution between abdominal and intercostal inspiration were detected only in the lateral posture.

10) The time required to produce fatigue (t_{lim}) of the diaphragm in three normal seated subjects breathing through a variety of inspiratory resistances was measured at functional residual capacity. The value of Pdi/Pdi_{max} that could be generated indefinitely (Pdi_{crit}) was approximately 0.4. The relationship between Pdi/Pdi_{max} and t_{lim} was curvilinear so that when Pdi/Pdi_{max} was small t_{lim} increased markedly for little changes in Pdi/Pdi_{max}.

11) Hypoxia (13% O_2) appeared to have no influence on Pdi_{crit} but led to a reduction in t_{lim} at $Pdi > Pdi_{crit}$ for equal rates of energy consumption.

12) Provided that the ratio of velocity of diaphragmatic shortening over the efficiency is constant, the rate of energy supply to the diaphragm increases as the rate of energy consumption increases breathing air. In contrast, under hypoxic conditions, the rate of energy supply remains constant, thus limiting the energy supply to the diaphragm and accounting for the differences in t_{lim} at equal energy consumption rates.

13) Maximum transdiaphragmatic pressure measured during a maximum inspiratory diaphragmatic effort with upper airways closed (diaphragmatic Mueller maneuver) gave higher

17) In most runs resulting in fatigue of the diaphragm or all the inspiratory muscles the subjects felt a dull pain in the area of the neck and shoulders parasternally and subcostally. All subjects experienced 'dyspnea' during trials in which fatigue resulted, while no dyspnea was reported during nonfatiguing runs. Most of the subjects experienced 'second-wind'. One subject frequently developed severe unilateral or bilateral abdominal pain identical to 'stitches'!

APPENDIX I

Quantity	SI Unit	Symbol	Expression in Terms of SI Base Units or Derived Units
Frequency	Hertz	Hz	1 Hz = 1 cycle/s ($1\ S^{-1}$)
Pressure	Pascal	Pa	1 Pa = 0.0075 mmHg
			1 Pa = 0.010 cmH_2O
Volume	$(metre)^3$	m^3	$1\ m^3 = 10^3$ decimetre
	$(decimetre)^3$	dm^3	$1\ dm^3 \doteq 1$ litre
Work	Joule	J	1 J = 9.807 Kg.m

APPENDIX II

α	-Energy stored in the muscle
Abin	-Abdominal inspiration
ADP	-Adenosine Diphosphate
A-P	-Anteroposterior
ATP	-Adenosine Triphosphate
β	-Rate of energy supply
C	-Energy consumption
$\dot{C}$	-Rate of energy consumption
CNS	-Central nervous system
CO_2	-Carbon dioxide
CV	-Closing volume
dPpl/dD	-Pleural pressure gradient
E	-Efficiency
Edi	-Electromyogram of the diaphragm
ECG	-Electrocardiogram
EMG	-Electromyogram
FE_{He}	-Expired Helium concentration
FFA	-Free fatty acids
FRC	-Functional residual capacity

He -Helium

HFT -High-oxidative fast-twitch

HST -High-oxidative slow-twitch

IC -Inspiratory capacity

IC_{in} -Intercostal inspiration

K -$\dot{V}di/E$

LFT -Low-oxidative fast-twitch

LA -Lactic acid

MVV -Maximum voluntary ventilation

N_2 -Nitrogen

N -Normal inspiration

O_2 -Oxygen

^{15}O -Radioactive oxygen 15

PC -Phosphocreatine or Creatine Phosphate

P_{CO_2} -Partial pressure of carbon dioxide

Pdi -Transdiaphragmatic pressure

Pdi_{max} -Maximum transdiaphragmatic pressure

Pdi_{crit} -Critical transdiaphragmatic pressure

Pes -Esophageal pressure

Pg -Gastric pressure

Pic -Pressure developed by the intercostal/accessory muscles

P_L -Transpulmonary pressure

Pm -Mouth pressure

Pm_{max} -Maximum mouth pressure

Pm_{crit} -Critical mouth pressure

P_{O_2} -Partial pressure of oxygen

Ppl -Pleural pressure

RD -Relaxed Diaphragm

RE -Relaxed Expiration

RV -Residual volume

SDH -Succinic acid Dehydrogenase

SE -Standard error

t_{in} -Total inspiratory time of a run

t_{lim} -Time limit, endurance time

TLC -Total lung capacity

TLC_r -Regional total lung capacity

V -Volume

$\dot{V}$ -Flow

$\dot{V}_A$ -Alveolar ventilation

VC -Vital capacity

V_D -Dead space

Vdi -Volume displacement attributable to the diaphragm

$\dot{V}di$ -Average flow attributable to the diaphragm

VDC -Voluntary diaphragmatic contraction

VDCE -Expiration with voluntary diaphragmatic contraction

$\dot{V}O_2$ -Oxygen consumption

$\dot{V}O_{2max}$ -Maximum oxygen consumption

V-P -Pressure volume curve

V_T -Tidal breath

U/L -^{133}Xe concentration in the uppermost 2 pairs to that of the lowermost 2 pairs of counters

W -Work

$\dot{W}$ -power

$\dot{W}_{crit}$ -critical power

^{133}Xe -Radioactive Xenon 133

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