The Effect of Training on Diaphragmatic Endurance and Fatigue in Quadriplegia

BY

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To the Sunshine of my Life,

my Husband, my Son, and my Daughter.

ABSTRACT

The effect of inspiratory resistive training on inspiratory muscle strength and endurance in quadriplegic patients was investigated.

At first it was demonstrated that diaphragmatic (Di) and intercostal (IC) muscle fatigue can be detected, reliably, by observing the changes in the power spectrum of the electromyogram (EMG) in normal subjects. The maximum inspiratory mouth pressure (Pm_{max}) in 6 quadriplegic patients was found to be 62 $\pm$ 16 cmH_2O. The critical Pm (Pm_{crit}), the pressure below which the EMG spectral modifications of fatigue were not observed, was found to be 10-21% of Pm_{max}. Pm_{max} and Pm_{crit} in quadriplegic patients was significantly lower than in normals. Patients underwent an inspiratory muscle training program for 16 weeks. Training produced significant increases in both Pm_{max} and Pm_{crit}.

It was therefore concluded that quadriplegics are predisposed to inspiratory muscle fatigue due to reduced strength and endurance. Inspiratory muscle training can increase both muscle strength and endurance, and protect them against muscle fatigue.

RESUME

L'effet de l'entraînement en résistance des muscles inspiratoires sur leur force et leur endurance, fut étudié chez un groupe de sujets quadriplégiques.

Il fut d'abord démontré que la fatigue des muscles intercostaux et diaphragme peut être détectée fidélement chez des sujets normaux en observant les changement de puissance dans la distribution de fréquence de l'électromyogramme (EMG). La pression inspiratoire maximale mesurée à la bouche (Pb_{max}) chez six (6) sujets quadréplégiques était de 62 $\pm$ 16 cmH_2O. La pression critique mesurée à la bouche (Pb_{crit}), pression sous laquelle aucun changement de puissance dans la distribution de fréquence de l'EMG n'est observée, variaient chez ces sujets entre 10% et 21% de la Pb_{max}. Pb_{max} et Pb_{crit} des sujets quadriplégiques étaient significativement inférieures à celles des sujets normaux. Après avoir été soumis pendant 16 semaines à un programme d'entraînement de leurs muscles inspiratoires, les patients quadriplegiques ont montré une augmentation de leur Pb_{max} et Pb_{crit}, à la fois.

Il est conclu que les quadriplégiques sont prédisposés à la fatigue des muscles inspiratoires due à une réduction de leur force et de leur endurance et que l'entraînement de ces muscles peut augmenter la force et l'endurance et prevenir ainsi la manifestation de fatigue.

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CHAPTER I

INTRODUCTION

I. INTRODUCTION

I.1 Introduction:

The respiratory system consists of two major components; a gas exchange organ (the lungs) and a pump (chest wall , and respiratory muscles to move gases in and out of the lungs). The lungs as an organ with gas exchanging function has been the primary interest of respiratory investigators for many years, while the pump function has been relatively ignored. In particular little attention has been given to the respiratory muscles and their reaction to sustained loaded conditions. This thesis focuses upon the behaviour of the respiratory muscles under such conditions.

Could the respiratory muscles ever become fatigued and therefore fail in much the same way as the heart would fail? This question was asked 43 years ago by Killick (163) and since then has been asked repeatedly. Skeletal muscle fatigue has been studied intensively and has been defined as the inability to maintain a predetermined load (266). Based on this definition, Roussos and Macklem (238) defined diaphragmatic fatigue as the point at which inability to sustain a predetermined level of transdiaphragmatic pressure occurred. Roussos et al (239) studied inspiratory muscle fatigue and defined it to be the point at which the subjects could no longer generate a predetermined mouth pressure. These two studies demonstrated that the inspiratory muscles can become fatigued and fail as pressure generators when sustaining loads at which the rate

of energy consumption exceeded the energy supplied. These results were similar to those observed in other skeletal muscles (207). It has been shown that a strong skeletal muscle is more fatigue resistant than a weak one (90,157, 168), and that increased load predisposes the weak muscle to fatigue faster than a strong one (258).

In trying to predict the development of respiratory muscle fatigue, a reliable and noninvasive means must be developed. Such methods are currently available for other skeletal muscles. Kogi and Hakamada (168), Kadefors et al (153) and Lindstrom (182) have shown that with the development of fatigue in the skeletal muscle, the amplitude of the lower frequency component (L) of the electromyogram increased while that of the high frequency component (H) decreased. In addition, Kogi and Hakamada (168) showed that the ratio of the two amplitudes (L/H) was independent of the muscle strength of contraction. But when the subjects performed fatiguing loads the ratio increased. This increase was proportional to the subjective symptoms of fatigue. Such changes in the frequency spectrum reflect a shift towards the low frequency activity (185). This technique, utilizing the analysis of spectral changes of the myoelectric signal for detection of fatigue should be applicable to the respiratory muscles. The demonstration of this has become an important objective of this thesis.

It is equally important to point out that the electromyographic signal of fatigue could easily be detected long before the muscle fails as a pressure generator, hence potentially applicable to clinical situations.

Patients with an increase in the work of breathing and/or a decrease in the inspiratory muscle strength, may be predisposed to the development of fatigue and its presumable result, acute respiratory failure (192). Groups of patients so predisposed include patients who have had a traumatic injury to their cervical segments. The mortality rate among quadriplegic patients is high and their prognosis is strongly influenced by respiratory complications (57,58,103,263). A decrease in inspiratory force, producing limited inspiratory capacity which accounts for a reduction in vital capacity were demonstrated to be characteristic of quadriplegic patients (26,101,103,125). The work of breathing in these patients has been shown to increase due to a reduction in lung and rib cage compliance (26,101,126). In addition, most of rib cage musculature is paralyzed, hence the whole load of ventilation must be carried by the diaphragm and sternocleidomastoid.

Leith and Bradley (177) demonstrated that normal subjects can improve their inspiratory muscle strength and/or endurance with a specific training program. Keens et al (159) confirmed these results in normal subjects and demonstrated improvement in patients with cystic fibrosis. In addition, they showed an improvement in ventilatory muscle

endurance with non-specific general upper body exercise. It was therefore reasonable to assume that patients with reduced ventilatory muscle strength and endurance, such as quadriplegic patients, should benefit from respiratory muscle endurance training programs, so that they could withstand an increased ventilatory load imposed on them during accute respiratory infection.

I.2 Purpose

The purposes of the work reported in this thesis are: a) to demonstrate that diaphragmatic and inspiratory muscle fatigue in normal subjects can be detected by utilizing spectral analysis of the electromyogram, a non-invasive technique which could provide an indication of fatigue before the inspiratory muscles fail as pressure generators. b) To determine the respiratory muscle strength and endurance in quadriplegic patients in comparison with normal subjects. c) To estimate the critical workload sufficient to produce fatigue in quadriplegic patients. d) To determine whether inspiratory muscle training can increase inspiratory muscle strength and endurance in quadriplegic patients and thus protect them against the development of fatigue.

CHAPTER II

REVIEW OF LITERATURE

II. REVIEW OF LITERATURE

This thesis is designed to demonstrate that weakness of the inspiratory muscles in patients, such as in quadriplegics, may lead to respiratory muscle fatigue when breathing against loads that are non-fatiguing in normal individuals. Respiratory muscle fatigue may be the primary cause of the high rate of respiratory failure in such patients. Thus, if respiratory muscle fatigue is diagnosed, it is reasonable to assume that these muscles could be trained to increase their strength and endurance. As a result of this, the resistance to fatigue would increase and improve the capacity of such patients to cope with increased loads.

With this goal in mind, the review of the literature is divided into eight sections.

1. Historical review.
2. Role of the respiratory muscles in ventilation.
3. Skeletal muscle fatigue and specifically its electromyographic detection.
4. Respiratory muscle fatigue.
5. The effect of training on skeletal muscle fatigue.
6. The effect of training on the respiratory system.
7. Respiratory complications and functions in quadriplegic patients.
8. Training of the respiratory system in quadriplegic patients.

II.1 Historical Review

In ancient China, 2000 BC "proper breathing" authority Lien Ch'i had already talked about the concept of breathing, that is, "transmitting the breath into a soul substance". He also discussed the vital essence of air (209). In 570 BC Anaximenes of Miletus stated that the essence of all things was air or pneuma (88). According to Wilson (290) the work of the Hippocratic Corpus (290) stated that the purpose of the respiration is cooling of the heat seated in the heart. They claimed that the air must be pumped to and from the lungs, via the auricles which act as bellows to pump air from the lungs through the pulmonary artery on the right and pulmonary vein on the left. They justified their theory by saying that when there is a wound the air escapes from the veins instantly and the blood flows thereafter. Later, in the second century AD, Galen, who disagreed almost entirely with the Hippocratic physiology and particularly with that of Errasistratus; showed that after section of the spine below the second cervical vertebrae of new born pigs, thereby cutting their phrenic nerves, respiration ceased. If section was done below the sixth vertebrae, he observed that isolated contraction of the diaphragm expanded the inferior parts of the thorax (290). Thus, the air fills the lungs because of the expansion of the chest. Galen understood that when the lungs are dilated they are filled with air and when the arteries are dilated they are filled with blood.

In addition, he maintained that the arteries are continually exchanging material with their surrounding, and that "In the whole body, the arteries communicate with veins and exchange air and blood with them by means of invisible openings" (290). However, Galen still maintained that the pumped air has a function of cooling the "heat seated in the heart". Leonardo da Vinci (88) disagreed with Galen and claimed that it was impossible for air to reach the heart. However, he agreed with the concept that air is inhaled because of the expansion of the chest wall and the lungs follow passively. He attributed the expansion of the chest wall to the intercostal muscle activity. His theory was that the lungs which touch the ribs from within must necessarily follow their expansion, thus, being like bellows drawing in air in order to fill the space which was formed. Vesalius actually observed the movement of the diaphragm during respiration as well as the ribs, and found that the diaphragm was responsible for the expansion of the thorax (77). The theory of air being pumped in and out of the lungs was fairly well accepted by this time and it was generally agreed that the lungs do not move naturally on their own and they are not expanded because they are filled with air, but they are filled with air because they are expanded. Magendi (77) claimed that diaphragmatic contraction depresses the viscera and the sternum as well as elevates the ribs. He also stated that the ribs must provide a resistance which is equal and opposite to the diaphragmatic force. The extent

of the elevation is proportional to the resistance of the abdominal viscera and the mobility of the ribs. These results were supported by Beau and Massiat (26) who, in addition, initiated the notion that women breathe differently than men in that they breathe with their rib cage as opposed to breathing with the abdomen. This notion has been refuted by Sharp et al (254) and Grimby et al (116) who observed no major differences in the relative contribution of the rib cage and abdomen between men and women, or between young and elderly during respiration. Duchenne (77) stimulated the phrenic nerves in laboratory animals and observed an expansion in the inverse and anteroposterior diameters of the rib cage.

II.2 The Role of the Respiratory Muscles in Ventilation

During the 20th century, particularly in the last two decades, several studies have been conducted in order to determine the role of the respiratory muscles in ventilation. Respiration is a rhythmical movement in which the diaphragm is inspiratory in function, and the abdominal muscles largely expiratory. The rib cage muscles, primarily the intercostals, are partly inspiratory and partly expiratory. Inspiration can also be assisted by the contraction of the accessory muscles. The rhythm of respiration is accomplished by agonistic and antagonistic actions of inspiratory

and expiratory muscles. Since Duchenne, the influence of the action of the diaphragm on the rib cage and the lungs was studied extensively and its actions are fairly well understood.

The Diaphragm: The diaphragm consists of three groups of fibers, the vertebral, the costal and the sternal. The vertebral fibers originate from the second and third lumbar vertebrae from the medial arcuate ligaments and from the lateral arcuate ligaments. The costal fibers originate from the side and upper margin of the lower six ribs and they interdigitate with the fibers of the transversus abdominis. Finally, the sternal fibers arise from the back of the xiphoid process. All three groups converge on the central tendon (3). It is generally agreed that the diaphragm is innervated almost entirely by the phrenic nerves. This has been shown in dogs (152,175,251), in goats (150), in cats (246) and in man (214,274,289); however, there are some reports indicating extraphrenic motor innervation (161). It has been demonstrated and generally agreed that the phrenic innervation branches out of the third, fourth and fifth cervical segments in man (3,128,175). The diaphragm is probably the principal muscle of inspiration (809,220,245). Sant'Ambrogio et al (245) showed that after bilateral phrenicotomy in the supine anesthesized rabbit, ventilation was reduced so markedly that arterial PCO_2 increased to 60 mmHg; ie, the intercostals and accessory muscles by themselves did not provide adequate ventilation.

An accepted theory has been proposed and elegantly elaborated by Goldman and Mead (110) as follows: During normal quiet breathing in man, only the diaphragm contracts during inspiration and it has two actions on the rib cage:

1) It pushes the viscera down and displaces the abdomen outward. In addition, a vertically upward force is developed. This force expands the rib cage. The contraction of the diaphragm displaces the rib cage along its relaxation line via the change in the abdominal pressure (Pab) while the fall in pleural pressure (Ppl) inflates the lungs. Their studies relating to this theory (110) also suggest that the inspiratory action of the diaphragm on the rib cage (rc) can be represented by the transdiaphragmatic pressure (Pdi) which is the difference between the abdominal and pleural pressure (Pab - Ppl). In addition, a decrease in Ppl, if it was the only force acting on the rib cage, should deflate the rib cage as well. This is not the case; therefore the transthoracic pressure could not possible represent the inflating force on the rib cage. Thus the Pdi is, in some way, transmitted into the rib cage.

2) It has also been demonstrated that in eviscerated animals, the diaphragm can have an expiratory action on the rib cage (71,77,110,205). The expiratory action was assumed by Goldman and Mead (110) to be expressed by (Ppl - Pb), where Pb is the pressure at the body surface.

The net action of the diaphragm on the rib cage, which is indicated by the pressure developed across the rib cage (Prc) is therefore given by the sum of the inspiratory and expiratory actions as expressed by:

$$Prc = (Pab - Ppl) + (Ppl - Pb)$$

Thus: $$Prc = Pab - Pb$$

The above considerations and equation lead Goldman and Mead to their hypothesis that in upright posture Pab is the effective pressure displacing the relaxed rib cage.

In addition, it was demonstrated electromyographically (EMG) that in spontaneously breathing cats and rabbits, the costal and vertebral parts of the diaphragm contract simultaneously (30,248). These data were corroborated by Lourenço et al (189) in dogs. The diaphragmatic EMG was clearly demonstrated to have a curvilinear relationship with the Pdi (117). Accurate measurements of diaphragmatic excursion and tension is important for the diagnosis of any abnormality or weakness, and an accurate and noninvasive technique should be applied. Such techniques could be the application of electromyographic measurements which reflect the muscle activity directly.

Intercostals: The external intercostals which are considered to be the muscles responsible for inspiration extend from the tubercules of the ribs to the costo-chondral junction and join the anterior intercostal membranes. The fibers slope obliquely downwards and forwards from the upper rib to the one below it (49). The intercostal muscles are

innervated by branches which arise from the first to the twelfth thoracic segments and the nerves are derived from the ventral primary ramus. Each intercostal nerve branches into external and internal intercostal nerves, separately supplying the two layers of intercostal muscles (253).

The function of the intercostal muscles has been a source of controversy throughout medical history and detailed examination of all the theories is not pertinent to this work. The accepted theory for many years was that proposed by Hamberger (127) which was based on a mechanical model and geometrical considerations. He claimed that when the external intercostals shorten they elevate the ribs and when the internal intercostals shorten they depress the ribs. However, this theory was not accepted by everybody.

Electromyographic recordings in anesthetized cats showed that behavior of the intercostal muscles was in accord with Hamberger's theory (10). These results have been confirmed in many animal and human investigations (167,213,253). Taylor (275) has largely resolved the issue by demonstrating electromyographically that the external intercostal muscles are purely inspiratory whereas the internal intercostals are expiratory. He has also shown that during quiet breathing the inspiratory intercostal activity is limited to the parasternal region. With increased size of the breath, the activity was shown to spread from upper spaces downwards (167). Viljanen (281) and Delhez and Petit (74) have shown that the EMG of the external intercostals,

recorded with surface electrodes in the sixth intercostal spaces in the mid clavicular line, has a linear relationship with the inspiratory muscular work and with the pressure developed by the inspiratory muscles. However, it seems that diaphragmatic activity may contaminate the results when the electrodes are attached to the skin at the sixth intercostal space. Paralysis of the intercostal muscles has been shown to contribute to a significant reduction in TLC and VC and ERV (53,101), demonstrating the significance of these muscles in ventilation.

Accessory muscles: The accessory muscles include the sterno-cleidomastoid (SCM) and the scaleni. In this work the SCM was measured and only its function will be reviewed. The SCM originates from the manubrium sterni and the medial part of the clavicle on the left and the right sides and is inserted into the mastoid process and occipital bones on both sides. Campbell (49) suggested that these are the most important accessory muscles of inspiration, however, this needs to be confirmed, the scaleni might be more powerful. The mechanical importance of these muscles is difficult to assess, however, anatomically they appear powerful. Their activity was observed during quiet breathing in patients with chronic airways obstruction and in quadriplegic patients. Duchenne (77) demonstrated a case with high cervical lesion of the spinal cord who breathed for some weeks with the SCM only. When he was given artificial ventilation because the patient was cyanotic the SCM activity ceased. The SCM activity was

investigated in very few studies, thus very little is known about the function of this muscle. Campbell and Friend (45) have shown that normally during quiet breathing, these muscles are not active.

When breathing entirely with the intercostal/accessory muscles the Pdi would be zero and the Pab = Ppl until the diaphragm developed a passive tension. Thus the decrease in Ppl during inspiration would not only expand the lungs but also suck in the abdomen, hence opposing the inflation of the lungs. The sucking in of the abdomen is a movement in the expiratory direction. It is therefore clear that breathing with the intercostal/accessory muscles in this way is inefficient (109,120) and the work of breathing is increased (109).

Interaction between the respiratory muscles: Despite the fact that the action of isolated respiratory muscles is well understood, the interaction between them is presently a source of lively controversy, specifically, between Goldman, Mead and associates (109,110,120) and Macklem and co-workers (191). According to Goldman and Mead's theory, the diaphragm always acts as an agonist. All of the pressure developed by the diaphragm at its pleural surface contributes to the inflation of the lungs, hence performs external work. The key to this is that since Pab is the effective pressure, changes in Pab are always responsible for other changes in the respiratory system. If Pab is negative the

intercostal pressure (Pic), in addition to displacing the rib cage, inflates the lungs. It is implicit from their analysis that the intercostal/accessory muscles cannot contribute to the transpulmonary pressure (Pl) swing unless the Pab is negative during inspiration. Therefore, if during inspiration abdominal muscles remain relaxed and there is no change in Pab, the diaphragm has to produce the pressure to inflate the lung, whereas the intercostal/accessory muscles have to produce the pressure to displace the rib cage. Consequently (Pdi + Pic) would equal the pressures developed across the rib cage and the lungs.

In contrast, Macklem et al (191) maintain that normally, during inspiration when the diaphragm is the only muscle contracting, its fibers shorten. During inspiration in which the only group of muscles contracting are the intercostal/accessory muscles and in which Pdi is zero, hence the decrease in Pab produces an inward displacement of the abdomen, the diaphragmatic fibers lengthen. However, in circumstances where the diaphragm contracts isometrically, it cannot perform external work. Thus, the work performed to inflate the lungs must be accomplished by the intercostal accessory muscles. Such an example could be when Pab does not change and the abdominal muscles remain relaxed while the diaphragm contracts. Macklem et al (191) suggest that under such circumstances, the diaphragm contracts quasi-isometrically hence not producing external work and

the intercostal/accessory muscles must supply all the pressure necessary both to inflate the lungs and displace the rib cage. Consequently, the sum of the Pdi and Pic would be greater than the total pressure developed across the lungs and the rib cage.

Furthermore, it was argued (191) that since the diaphragm has performed no work, it acts as a fixator, preventing the transmission of Ppl to the abdomen resulting in expiratory inward abdominal movement. This means that the diaphragm does not always act as an agonist. Because of the differences between the two analyses, it could be predicted that the calculations of the work performed by the diaphragm or intercostal accessory muscles will produce different results depending on which analysis is employed.

It is implicit that the evaluation of the action of the respiratory muscles on the rib cage and lung in patients with spinal cord injury is very important and understanding of the mechanism involved is critical to understanding the consequences of paralysis.

Summary

The history of respiratory research goes as far back as 2000 BC. The general theories of respiration were such that air is essential for life and it is pumped into the system. Until the time of Leonardo da Vinci (88) it was thought that air could reach the heart. He demonstrated that air is pumped in and out of the lungs by the contraction of the respiratory

muscles, ie. the diaphragm and intercostals were responsible for the expansion of the rib cage which in turn, causes the lungs to be filled with air. The contraction of the diaphragm had already been observed to expand the base of the thorax by Magendi, Beau and Miassiat and later on by Duchenne. The action of the diaphragm on the rib cage was very elegantly elaborated by Goldman and Mead who showed that in normal quiet breathing the diaphragm is the only contracting muscle which inflates the lungs and it has two actions: 1) Pushes the viscera down, displaces the abdomen, and expands the rib cage to the extent that abdominal pressure increases. The Pdi was demonstrated to represent the diaphragmatic tension and it is given by (Pab - Ppl). Since the pressure applied by the rib cage muscles, ($Pmus_{rc}$) is applied across the rib cage and the lungs ΔPmus would be equivalent to $\Delta P_{rc} + \Delta P_L$. 2) The diaphragm was demonstrated to have an expiratory action as well as inspiratory action, and that the net diaphragmatic action is the sum of the inspiratory and expiratory pressures developed due to the diaphragmatic contraction.

In addition, the diaphragm was shown to contract as a unit, and Pdi was demonstrated to have curvilinear relationship with the diaphragmatic myoelectric activity. A reduction in maximum Pdi may reflect diaphragmatic weakness or paralysis. Thus, it is reasonable to assume that if weakness in this muscle exists fatigue would be developed and this might lead to respiratory failure.

The intercostal muscles which are located between the ribs were demonstrated to have a secondary importance in the function of ventilation. Paralysis of these muscles lead to a significant reduction in respiratory volumes. This reduction points out the significance of these muscles in ventilation. During quiet breathing intercostal activity is limited to the parasternal region and with increased volume the activity spreads from the upper spaces downwards. Very little is known regarding the function of the accessory muscles except for the fact that they are not active in quiet breathing in normal subjects, and they are highly active during quiet breathing in patients with high cervical cord injury and patients with chronic airway obstruction. Weakness in any of the inspiratory muscles, which are essential for ventilation may lead to reduced ventilatory capacity and perhaps predispose these muscles to fatigue.

The issue of the interaction between the diaphragm and the intercostal/accessory muscle is presently a source of controversy between Goldman, Mead and co-workers, and Macklem and co-workers. The fundamental differences are:

According to Goldman and associates the diaphragm always acts as an agonist. Conversely, Macklem et al argue that it could act sometimes as a fixator and sometimes as an agonist or both.

Goldman and Mead suggest that it is only after the intercostal accessory muscles provided the pressure necessary to inflate the rib cage that they can contribute to lung inflation. Whereas Macklem et al state that the contraction of rib cage musculature cannot inflate the rib cage without simultaneously inflating the lung.

Because of these differences the calculations of the work done by each muscle would be different depending on which analysis is being used.

II.3 Skeletal Muscle Fatigue

Fatigue is a complex phenomenon which refers to a variety of physiological and psychological events. Fatigue can be acute, caused by excessive use of an organ or a general body system; or chronic, which may arise from repeated acute fatigue (115). The general nature of fatigue involves a sensation of bodily tiredness, weakness, reduced motivation, etc. On the other hand, local fatigue is caused by excessive use of an organ or a muscle. Muscle fatigue is the focal interest of this review. The site of muscular fatigue may be located anywhere along the chain of muscular contraction, from the central nervous system to the contractile apparatus. For many years physiologists have debated the question whether muscular fatigue is central or peripheral in origin (156,181,198,266). Inhibition of the synaptic connection as a site for fatigue, as well as central fatigue have been excluded (198). Stevens and Taylor (269), however, have presented data which shows that the changes indicating fatigue during maximum voluntary contraction occur in the myoneural junction during the first minute and subsequently appear in the contractile element. This evidence, nevertheless, suggests that fatigue is due primarily to failure in some parts of the peripheral apparatus, namely the muscle; particularly when submaximal loads are sustained.

This review will concentrate on describing the changes known to occur in skeletal muscles during sustained contractions leading to acute local fatigue. Specific attention will be given to the electrophysiological modifications that occur with skeletal muscle fatigue and the means of detecting it. In particular, the utilization of electromyographic techniques in diagnosing skeletal muscle fatigue and the use of spectral analysis of the myoelectric signal will be described in detail.

The continued contraction of a muscle against a fatiguing load is associated with a sequence of events including biochemical changes related to fuel supply, energy consumption and electrophysiological changes produced by the fatiguing process (186). As a result,maintenance of a given tension by voluntary contraction necessitates progressively greater effort until an end point is reached when the tension begins to fall. At this point the muscle fails to attain or maintain the contraction achieved initially. Consequently, skeletal muscle fatigue, thus far, has been defined as the inability to attain or maintain a predetermined tension or load (15,266). Skeletal muscle fatigue can result from a sustained contraction such as isometric contraction or repeated short contractions of a dynamic nature.

As shown in Figure 1, maximal isometric force can be sustained for only a few seconds; 50 percent of maximal force for about one minute; and at loads below 50 percent, the endurance time increases rapidly. This force endurence curve has been shown to be exponential (233). It is possible to sustain isometric force at a level of 15 percent of maximum force or less for hours as demonstrated by Romhert (233) and this percentage level is the upper limit of the load that could be sustained isometrically for indefinite periods of time (33,257). However, there are variations in the endurance time results depending on the muscle group studied, fiber composion within the muscle, and individual variations in the maximal strength (15). Force expressed as percent of maximum implies two separate factors. 1) Strength: Strength of contraction in relation to the maximum force. 2) Load: Sustaining a contraction at a certain percent of maximum implies sustaining a load which is a certain proportion of the maximum capacity. The higher the load the more it influences the development of fatigue.

In the case of dynamic intermittent contractions the endurance time depends on the level of load and the duty cycle. The latter is the fraction of time the muscle spends contracted and thus is the ratio between contraction time and total time. The longer the duty cycle the shorter is the endurance time (232), the greater the production of lactate, and the greater use of anaerobic energy source in force generation (14).

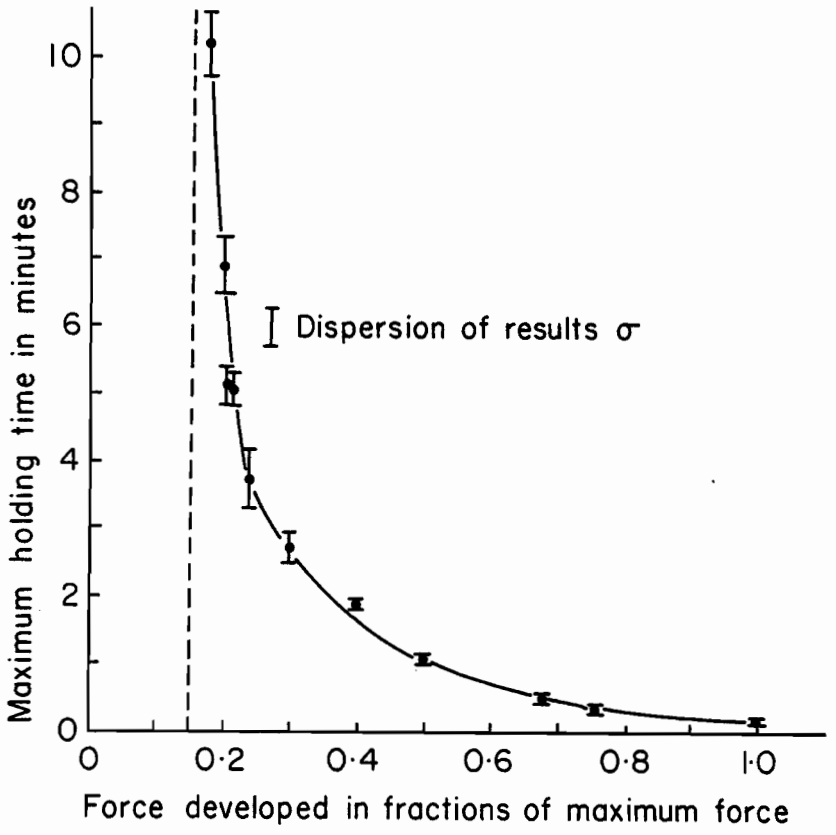

Figure 1: Maximal work time in minutes versus force in isometric contraction. The load expressed in percentage of maximal isometric strength. The averages of the results (closed circles) obtained in studies on different muscle groups in 21 subjects. The level of work that could be sustained indefinitely marked by dashed line (From Rohmert, 233).

The energy sources stored and readily available within the muscle are very limited. The supply from a breakdown of ATP available which is very rapid, would cover only a maximal effort of about one second; and the generation of ATP from the breakdown of all the phosphocreatine would cover another few seconds of maximal effort (15). It is well established that maximal effort can be mainted for less than 10 seconds because "rapid energy" is no longer available at the end of 10 seconds due to exhaustion of prosphocreatine and eventually also ATP. Some of the immediate energy would come from glycogenolysis which is increased during effort giving rise to increasing amounts of lactate (13).

Ischemia results in a more rapid development of fatigue and sensation of pain (232). The energy sources are supplied to the muscle via the blood. Therefore during ischemia when there is a complete interruption of blood flow to the muscle, there is no oxygen delivery and the total energy sources are reduced. Consequently, the active muscle must derive its energy from anaerobic source. Lactic acid accumulates rapidly and endurance diminishes (258). Accumulation of lactic acid results in increased acidity in the muscle tissue which contributes significantly to the development of fatigue and the sensation of pain (210,230,232,258). During isometric contraction below 15 percent of maximum, little impairement of blood flow occurs. However, between 15% and 70% of maximum effort, there is a progressively greater

interruption of blood flow to the active muscles which is maintained throughout the duration of contraction (258).

During dynamic contraction when the duty cycle is 0.5 so that contraction and relaxation times are equal, skeletal muscle fatigue will occur while generating tensions greater than 40 percent of maximum force (16,266). The critical load in isometric contraction is obviously less than during dynamic contractions, under which the restriction of blood flow is not continuous. Consequently in isometric contraction energy consumption is greater, and energy supplies are less than in dynamic contraction. At 70% of maximum effort, the blood vessels are completely occluded and all metabolism is anaerobic (210), hence predisposing the muscle to fatigue and causing reduced endurance time. It is therefore clear that the blood flow to the contracting muscle has an influence upon the energy consumption to energy supply relationship. At higher levels of contraction with restricted blood flow, the oxygen needed by the muscle will exceed the oxygen supply and the anaerobic processes must contribute markedly to the energy yield. Skeletal muscle fatigue was demonstrated to occur when the rate of energy consumption by the muscle was greater than that supplied to the muscle by the blood (207). Consequently the contracting muscle does not have any further sources of energy and it fails as a force generator.

At a given energy expenditure, the glycogen stores will be depleted at a much faster rate when the muscles must work anaerobically than when they can work aerobically. Efficiency is determined by the rate of energy consumed per unit of work performed, namely if more energy is consumed per unit of work, the efficiency is reduced. During anaerobic contraction the muscle consumes 13 times more energy than during aerobic activity (15). This implies that anaerobic work has a lower efficiency than aerobic work. If energy stores are consumed and the demands for energy can no longer be met the muscle can no longer contract, i.e., fatigue occurs. Monod and Scherrer (207) derived an expression relating the development of muscle fatigue to the total amount of energy consumed, based on experimental findings obtained during dynamic work of the biceps and quadriceps muscles at different levels of intensity. They stated that the total energy (C) consumed while performing work which leads to exhaustion at a given endurance time (t_{lim}) is equal to the rate of energy supplied to the muscle (β) multiplied by t_{lim}, and to the energy stored in the muscle (α).

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

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

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

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

The factors which are important in the development of muscle fatigue, therefore are: a) the tension developed or force produced by the muscle; b) the maximum tension generating capacity of the muscle; c) the energy stored and readily available within the muscle; d) the energy supplied to the muscle which is a function of its perfusion, the oxygen content, and concentration of substrate within the arterial blood; e) the efficiency of the muscle to perform external work (207,238).

The Contractile Mechanisms and the Electrophysiological Properties of a Skeletal Muscle:

The functional element of a mammalian striated muscle is the motor unit (249). This unit consists of a number of muscle fibers which are innervated by a single motor neuron.

The cell body of the motor neuron is located in the anterior horn of the spinal cord, and its activity is controlled either voluntarily from the cortex of the brain or by reflex arcs of varying complexity. From the spinal cord the motor neuron transmits impulses to the muscle fibers via the motor end plate, also termed the myoneural junction. Near the point of muscular innervation, each motor neuron branches into nerve fibers of different length which give rise to both temporal and spatial dispersion of the arrival of the triggering pulses. Fibers belonging to one motor unit may be mixed with fibers from several other motor units. The number of fibers per unit ranges from 5 in small

muscles such as found in the eye, to several thousand in the large skeletal muscles (24). The motor end plates are located in the middle of the muscle fibers. When the impulse arrives at the motor end plate it causes a release of acetylcholine, producing biochemical and enzymatic reactions which result in depolarization of the muscle cell membrane. The amplitude of the depolarization is approximately 70 mv. These signals are known as action potentials (64,143), which are generated and dissipated into the surrounding tissue (24). They also propagate along the muscle fibers at a velocity of 2 to 5 meters per second (182,210,288) and release mechanical twitches which make up the muscular contraction. A strong contraction of a skeletal muscle requires the contraction of many motor units. In order to produce this, the asynchronous volleys of impulses coming down from many axons results in complete asynchrony of the contracting fibers. The result is a continuous shower of individual muscle fiber twitches at different frequencies and dispersed in space and time resulting in a smooth contraction. When contractions become synchronized, the tremor seen in certain pathological conditions, results.

These events produce myoelectric signals detectable by the electromyogram (EMG). Since the EMG portrays electrical signals due to muscle contraction, any myoelectric changes that occur in the muscle due to fatigue should also be reflected in the EMG signal.

EMG Changes During Muscle Fatigue: In moderate levels of contraction, there are so many units being activated that the myoelectric signal has a character of noise (219). It follows that appropriate means of analyzing the EMG data are necessary in order to diagnose fatigue. The EMG of fatigue has been investigated for many years and different techniques were developed.

Electric potential from voluntarily contracted skeletal muscles were first recorded by Piper (226) by means of an "Einthoven String Galvanometer". He used electrodes that could be applied to the skin and found that fairly regular waves of 47-50 Hz were the predominant phenomenon in medium to strong contractions. The existence of this rhythm, termed Piper rhythm, is easily varified and has been confirmed by many other investigators (24,65,248). Piper himself observed (226) a decrease in the carrier frequency related to this rhythm, in connection with sustained strong isometric contraction, reflecting the development of fatigue. The changes in the Piper rhythm with respect to fatigue were again reported in 1923 by Cobb and Forbes (65) who documented fatigue of the wrist flexors. This fatigue, primarily that of the flexor carpi radialis, is associated with an increase in the EMG amplitude and a decrease in the Piper rhythm frequency while the magnitude of the force generated by these muscles leveled off or decreased. They concluded that fatigue occured at the myoneural junction. However, the evidence demonstrating an increase in the amplitude of the

myoelectric activity and a decrease in the frequency during sustained submaximal contractions was confirmed by other authors (76,84,169,186,248). They attributed the observed changes to a) recruitment of other motor units to compensate for a decrease in the contractile force of the fatiguing units, and b) synchronization phenomena, namely grouping of action potentials. Person and Mishin (224) using computerized techniques to analyze the action potentials of different parts of the muscle during fatiguing contractions confirmed that synchronization indeed occurs.

Clarke, Hellon and Lind (63) gave a more detailed description of the time course of the integrated EMG (IEMG) during fatiguing contractions. The IEMG was found to rise slightly during the first half of the fatiguing contraction and then rose steeply until complete fatigue was reached. The steep rise in the IEMG appeared when the tension began to show a decrement. The rise in IEMG was interpreted to be due to recruitment of muscle fibers as fatigue developed, and that all or nearly all available fibers were activated by the point of fatigue. This theory was supported by the fact that an increase in temperature from 27° Centrigrade to 35° Centigrade was found to shorten the contractile time, i.e. endurance, but the total IEMG at the point of fatigue was similar for the two temperatures. In addition, the slope of the IEMG increase is dependent on the level of load being maintained (283).

Other reports demonstrated either no change in the action potential frequency with fatigue (30), or a decrease in motor unit action potential amplitude (186) and an increase in action potential duration.

The shape of the fatigue curve, utilizing the changes in IEMG as a function of time, was described slightly differently by different investigators. Edwards and Lippold (84) have found that "during the fatiguing contraction, the electrical activity (by which they mean amplitude) always fell during the first minute...", while De Vries claims that this initial reduction is an artefact "which results from an unnecessary level of tension generated through co-contraction of agonist and antagonist by subjects not thoroughly familiar with the procedure" (76). The shape of IEMG curve in relation to time might vary with different loads (76), namely, when low loads are sustained most of the curve has a linear shape, and the shape is more cirvilinear when high loads are sustained (76).

The curve describing the IEMG in relation to time was generally curvilinear (76,186). It is possible to analyze the EMG signal described by De Vries (76) and Lippold et al (186), in terms of changes in the amplitude and frequency of the action potentials in relation to time. An increase in both parameters contributes to an increase in the overall integrated signal of the EMG, however the analysis does not allow the distinction between the two. The myoelectric signal has a

character of random noise, even in moderate levels of contraction. Therefore, an analysis applied to any electrical noise could be used, namely analyzing the frequency spectrum of the myoelectric signal.

Spectral Analysis: If a signal is subjected to frequency analysis it is basically subjected to a Fourier analysis which deals with the distribution of the power spectrum. In this analysis the EMG signal is broken into a number of pure sine waves of varying frequencies. The amplitude of each sine wave is measured and plotted against frequency unlike IEMG which was plotted against time. The Fourier analysis sums the amplitude of all the waves within every frequency range and then relates amplitude to frequency as shown in Figure 2. The term "frequency" in this context has a strict and unambiguous meaning: "The number of periods of sine curves falling within a time unit" as opposed to the number of impulses within a time unit, which is the Piper rhythm. Power spectrum analysis, namely the analysis of the distribution of amplitude as a function of frequency, was first used for analyzing the EMG by Walton (286). Since then, interest in such techniques for EMG analysis has been accelerated particularly in the last decade.

The power spectrum of the EMG has been demonstrated to have a maximum peak at frequencies ranging from 10 Hz to about 100 Hz when surface electrodes are used, and from 100 Hz to 200 Hz when the myoelectric activity is recorded by

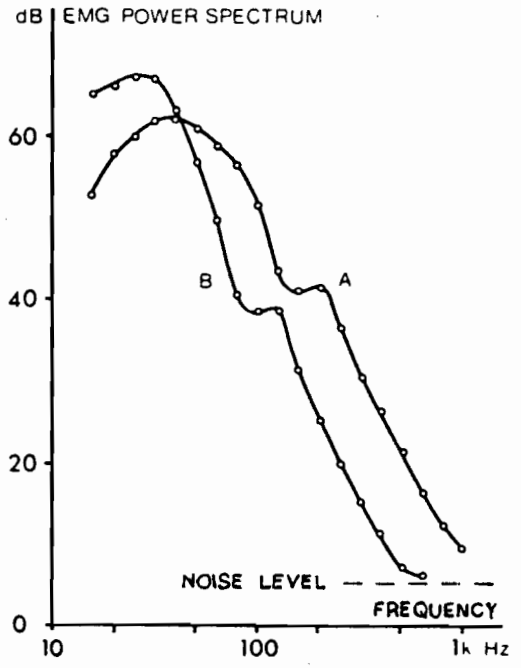

Figure 2: EMG power spectra obtained at 2 kilopond loads: A) before, and B) after 30 seconds of maximum loads (from Lindstrom et al, 185).

needle electrodes (89,153,154,182,286).

The factors influencing the normal shape of the distribution of the power spectrum were shown by different investigators to be: 1) The resistive and dielectric properties of the electrodes, the tissue, and the electrode tissue junction (40,153,183). 2) The repetition rate of the motor unit discharge (89) and the number of fibers in a unit. 3) Synchronization of motor unit activity (89,182). 4) The shape and duration of the motor unit signal (154). 5) Conduction velocity (210 , 6) Other factors include electrode geometry with respect to the source of activity (153,185,247) and type of electrodes (153).

A very significant factor which was found to change the shape of the power spectrum was skeletal muscle fatigue. Kogi and Hakamada (168) have shown that,with the development of fatigue in skeletal muscle , there is a decrease in the amplitude of high (H) frequency components and an increase in the amplitude of low (L) frequency components of the myoelectric signal recorded by surface electrodes. They demonstrated that the amplitude of the components of the power spectra which was less than 40 Hz increased with fatigue, while that from 40 - 120 Hz decreased, so that the ratio of the two (L/H) increased progressively as fatigue developed. The increase in the ratio L/H when the biceps muscle performed fatiguing work loads was apparent substantially before the limit of endurance had been reached. Although there was considerable inter- and intra-individual variability the L/H

ratio was shown to be virtually independent of muscle force. When the muscle sustained non-fatiguing loads these authors observed no change or little change in the L/H ratio. Furthermore, Kogi and Hakamada (168) correlated the subjective grading of fatigue to the changes in the low to high frequency ratio and found an excellent correlation between the two parameters. In stage one (sensation of fatigue in the muscle) the L/H ratio increased by 20-40%; in stage 2 (development of local pain) the ratio increased by 20-60%; in stage 3 (desire to relax the contraction) the ratio increased by 30-100%; and in stage 4 (incapability of maintaining the tension) the L/H ratio increased by 50-200%. These results were corroborated by Lloyd (188) who demonstrated that the shift in the power spectrum during fatigue correlated well with the grade of muscle pain that was sensed by the subjects. This study by Kogi and Hakamada is an important landmark in that the EMG signal of fatigue was detectable before the muscle failed as a force generator. Subsequently Kaiser and Petersen, (154) and Sato (247) reported a decrease in high frequency content during strong fatiguing contractions. A most detailed investigation of the myoelectric spectral changes that occur with fatigue was carried out by Kadefors et al (153).

They demonstrated that when the biceps brancii muscle sustained a load above 10 percent of maximum isometric strength there was always an increase in the amplitude of the low frequency content and a decrease in the high frequency content. Furthermore, they showed an increase in the total power and a shift in the power distribution towards the low frequencies, similar to that described by Lindström et al (185) (See Figure 2). In addition, a progressive decrease in the ratio of the amplitudes of the high (H) (200 Hz) to a low (L) (50 Hz) frequency components (H/L) with time was observed. The changes were more pronounced for records obtained by needle electrodes than for surface electrodes. These findings corroborate those of Kogi and Hakamada (168) and Sato (247). The shift from a high frequency towards the low frequency activity of the power spectrum during fatigue has been shown by various investigators in the last decade (40, 153, 154, 168, 170, 182). Various explanations for such changes have been given by many authors over the years. Lindström et al (185) proposed that the shift of the power spectral activity towards the low frequency is due to a decrease in the muscle fiber conduction velocity of the action potentials. A decrease in conduction velocity with the development of fatigue was demonstrated by Mortimer et al (210). This in turn was attributed to an intramuscular accumulation of lactic acid when the threshold for

anaerobic metabolism was exceeded and blood flow is restricted. Humphreys and Lind (141) have shown that intramuscular pressure indeed occludes the blood flow to the muscle at higher tensions. Karlsson (155) demonstrated the the decline in lactic acid in the muscle, after exercise, has a time constant approximately equal to the time constant of the conduction velocity recovery. Lindström (182) showed that conduction velocity can decrease by as much as 40 percent before the muscle is completely exhausted. The shift in the power spectrum with fatigue was also attributed to dysfunction of muscle spindles (170) and synchronization of the motor units' activity (24, 153, 224, 247).

Synchronization is explained as follows: All muscle fibers of a motor unit do not contract at exactly the same time, some being delayed for several milliseconds, hence the electrical potential developed by a single twitch of all fibers in the motor unit is prolonged. When a contraction occurs there must be complete asynchrony of motor unit contractions imposed by asynchronous voltage of impulses coming down many axons. Thus, all the motor units are contracting and relaxing at different rates of up to approximately 50 sec. The result of a continuous shower of twitches with different frequencies within the muscle is a smooth contraction. With fatigue, synchronization begins to occur, i.e., more and more fibers will have the same frequency, and will contract at the same rate, resulting in a visible termor. Furthermore, synchroni-

zation of the action potential firing produces a delay in the twitch which may contribute to the increase in the amplitude of the low frequency activity: As a consequence there is a decrease in the H/L ratio, which reflects a shift in the power spectrum distribution towards low frequencies.

An interesting and attractive explanation for the modifications in the power spectra when sustaining submaximal fatiguing load is the recruitment of new motor units as the original ones are exhausted (153, 168). The recruitment is primarily of slow motor units, contributing to the shift in the frequency spectrum towards the low frequency activity. The high frequency and low frequency modifications of the power spectra, due to fatigue, are not of the same origin (168, 185, 210). The modification in the high frequency component of the power spectra are generally attributed to changes in the conduction velocity (184, 185); while the increase in the low frequency activity are generally attributed to recruitment of slow motor units and synchronization (168).

The centroid of the power spectra distribution is the frequency which reflects the relative contribution of the low and high frequency component of the power spectral distribution. The centroid was demonstrated to decrease with time when a fatiguing load is prolonged (184).

Spectral changes and muscle fiber composition: A skeletal muscle generally consists of three main fiber types: 1) slow twitch, high oxidative fibers (SHO) which are fatigue resistant 2) fast twitch, low oxidative fibers (FLO) which fatigue fast, and 3) fast twitch, high oxidative fibers (FHO) which fatigue slowly (46). A high positive relationship between endurance time and the proportion of SHO was observed (142). The endurance time was shown to be longer in muscles with higher proportion of SHO fibers (142,282) than muscles with predominantly FLO and FHO fibers. The high oxidative fibers were also shown to have higher resistance to fatigue (90). When sustaining a high fatiguing load the mean power frequency (MPF) namely, the mean value of amplitude at all frequencies decreased significantly faster in subjects with a higher percent of FLO fibers in their vastus lateralis muscle, than subjects with higher percent of SHO fibers. In man (90,113) glycogen depletion in the vastus lateralis after submaximal exercises occurs in faster type fibers first and later in slower type fibers. A direct connection between the reduction of the conduction velocity and a shift to lower frequencies in the EMG spectrum has been observed (185, 210). Mortimer et al (210) have also reported a greater slowing of action potential wave in predominantly faster type muscle (gastrocnemius) versus slow muscle (soleus) in cat, under conditions of occluded blood flow and continued electrical stimulation on motor nerves supplying these muscles. Komi and his co-workers (personal communications) are currently collecting data which point out

the possibility that it is reasonable to expect that high frequency activity reflects primarily activity recorded from fast twitch fibers. However, there is no other experimental evidence to support this theory and much work is still needed in this area.

Summary

During voluntary contraction human skeletal muscle at submaximal or maximal levels of force, acute local fatigue may be developed. When isometric or repeated maximum force is sustained a reduction in the force level with time is observed. The generally accepted definition of muscle fatigue is the inability to attain or maintain a predetermined force. However, if muscle fatigue plays a role in clinical situations, an early and reliable diagnosis is necessary. Analysis of the myoelectric potential provides a means for detecting fatigue in a skeletal muscle. If submaximal loads are maintained for long periods IEMG increases and the slope of this increase depends on the load maintained. In addition, muscular fatigue causes a shift in the EMG frequency spectrum, a shift that results in augmentation of the amplitude at the lower spectrum range with a concomitant reduction in the high frequency content. The shift has been attributed primarily to a reduction in conduction velocity which probably causes the reduced amplitude in the high frequency content and recruitment of new motor units which may cause the increase of amplitude in the low frequency

range. There is some indication that the frequency spectral changes with fatigue may also be related to the fiber composition of the muscles. The power spectrum shift was observed almost immediately after a fatiguing contraction started, thus it has an advantage of detecting fatigue sufficiently early before the muscle fails as a force generator. Spectral analysis was therefore chosen as a technique to detect inspiratory muscle fatigue.

II.4 Respiratory Muscle Fatigue

Fatigue is generally defined as the inability to maintain a predetermined load; in this case the inability to produce a certain level of transdiaphragmatic pressure (Pdi), or mouth pressure (Pm).

Skeletal muscle fatigue is thought by many to occur when the rate of energy consumed by the muscle is greater than the energy supplied to the muscle by the blood (207). Under these conditions the muscle has an inadequate source of energy so that it fails as a force generatore (207). Since the respiratory muscles act as force generators, can they ever become fatigued and fail in much the same way as other skeletal muscles?

Early in this century Rehns (229) and Lee et al (176) considered the possibility that the respiratory muscles could become fatigued. They studied the fatiguability of the diaphragm following electrical stimulation of the phrenic nerve and concluded that the diaphragm is stronger and more resistant to fatigue than other skeletal muscles. However, in contradiction, Stigler (270) observed signs of fatigue of the respiratory system in subjects who were asked to breath under water through tubes which must have provided a great resistive load. The signs of fatigue were determined when subjects started to take deep breaths which were subsequently followed by rapid shallow breathing. He stated that "finally the signs of fatigue of respiration as such

become more frequent and breathing became more shallow until a point that the subjects could not sustain the ventilation under water any more" namely, there was a limit to the respiratory muscles' capacity to function. In addition, in 1935 Killickstudied the effect of resistance on the respiratory system and suggested that the important factor in the production of respiratory failure which results when breathing through an excessive resistance is fatigue of the respiratory muscles (163). This was the first time that the possibility of respiratory muscle fatigue as a cause of respiratory failure was suggested. Since then this possibility has arisen frequently. Nevertheless, very few attempts have been made to document respiratory muscle fatigue in either health or disease, in either man or experimental animals. Comroe (66) pointed out that the maximum voluntary ventilation (MVV) achieved in 30 sec could not be sustained for a period of several minutes. More recently, a 4-5% reduction in voluntary ventilation has been demonstrated in the first minute of testing. This has been attributed to fatigue and the test has been shortened to 20 sec, and 15 sec (67). Tenney and Reese (276) demonstrated that the maximum voluntary ventilation that could be sustained for 15-20 sec fell rapidly with time up to two minutes but then more slowly thereafter. 65% of MVV was sustained for 4 minutes and 53% MVV for 10 min. The results obtained by Tenney and Reese were similar to those found in other studies (95,177,259,291). In these studies isocapnic condition

was maintained by replenishing CO_2. However, the range of the critical MVV's, namely, the MVV which could be sustained indefinitely was quite large (50-80% of maximum). Zocche, Fritts and Cournand (291) reported that the maximum hyperventilation that could be sustained for 15 min was 53% of the MVV. This variability could be related to a) the cooperation of the subject in performing the test, b) the level of fitness of the subjects being used and c) technical factors such as equipment resistance. Freedman (95) observed changes in the pattern of breathing with time during a prolonged MVV test, specifically an increase in the frequency of breathing was observed between the first and the fourth minute. He attributed this to: a) a fall in the compliance, b) fatigue of the respiratory muscles and c) that the subjects were hunting for more comfortable combination of rate and depth in the first minute and settled on this in the fourth. In discussing the factors limiting sustained ventilation, it was suggested (95) that the respiratory muscles cannot exert the same power for long periods of time as for short periods. Although he did not consider fatigue of the respiratory muscles to be the primary limiting factor, direct observations of the performance of the respiratory muscles as a possible limiting factor during MVV were made on two subjects, in whom esophageal and gastric pressure were measured during an attempt to keep up a target ventilation close to the 15 sec MVV. At the point at which a fall in the level of ventilation was observed

peak esophageal pressure fell during inspiration. The fall was small in magnitude but might have been sufficient to account for the inability to sustain a level of ventilation so close to maximum. A subjective sensation of discomfort localized in various muscle groups also pointed out the possibility that a decline in the power of the respiratory muscle was a limiting factor. Freedman (94) showed an increase in blood lactate concentration after 4 minutes of MVV, indicating that some anaerobic work was being done. Anaerobic work has been shown in other skeletal muscles to be less efficient than aerobic work (15,60) because it imposes higher energy consumption on the muscle.

In order to estimate maximum inspiratory muscle strength an assessment of the maximum force that the patient could develop is necessary. Consequently, the level of load being sustained as percent of maximum could be evaluated for direct measurements of the respiratory muscle endurance, in order to test the possibility that respiratory muscle fatigue is a limiting factor in breathing, in exercise and that it might be a cause of respiratory failure as suggested by Killick (163) and then by Sharp et al (256). Goldberg et al (108) found inward abdominal displacement in inspiration in 5 of 20 patients who were not in respiratory failure but in 8 of 10 patients who were in respiratory failure. They concluded that "faulty coordination of overworked and fatigued respiratory muscles contributes to dyspnea and respiratory failure". Lieberman et al (179,180) assumed that the

diaphragm is the primary inspiratory muscle at all levels of inspiratory activity, and that phenomenon of fatigue in terms of metabolic processes is largely dependent on the relative contribution of the white versus red fibers with the red fibers being less vulnerable to fatigue. Therefore, they tested the possibility that the decrease in ventilation during prolonged MVV maneuvers is related to fatigue of specific muscle fiber types in the diapragm. They were the first to investigate this possibility. When supramaximal stimuli were administered to the guinea pig's diaphragm a steep drop in tension was observed in the first 5 minutes followed by a slower decline to a steady state tension. The curve was similar in shape to that described by Tenney and Reese (276) in which the decline in MVV was measured as a function of time. They also tested the fiber composition of a guinea pig's diaphragm and found that there were three different muscle fiber types: 1) fibers which did not fatigue (high oxidative - slow twitch), 2) fibers that fatigued slowly (high oxidative - fast twitch), and 3) fibers that fatigued fast (low oxidative - fast twitch). This fiber composition is similar to that described by Burke et al (46) in the gastrocneimus muscle. Consequently Lieberman (180) suggested that the rapid decline in tension during the first 5 minutes was related to rapidly fatiguing fibers the slow decline up to 10 minutes is related to the slow fatiguing fibers and that the nonfatiguing fibers maintained the tension beyond the 10 minute period. They cor-

related fatigue and the histochemical characteristics of myofibrillar ATPase and SDH activity and did not establish a causal relationship. But the results were consistent with the hypothesis that fatigue of the diaphragm results from a faster rate of ATP depletion than the rate of ATP synthesis. To relate the data on human subjects during maximum voluntary ventilation which shows an exponential decrease in MVV with time, they assumed that the relation of fatigue to histochemical characteristics is the same in human as in guinea pigs. For this purpose samples for muscle biopsies were taken from the ventral regions of the diaphrgm in seven males who were undergoing thoracic surgery. The second assumption was that human subjects in MVV recruit all the motor units of the diaphragm (an assumption that needs to be proven).

The evidence provided by Lieberman et al (179,180) is very important in understanding diaphragmatic fatigue. However, it has left us with a need to investigate the existance and diagnosis of respiratory muscle fatigue in human subjects and to substantiate the hypothesis that respiratory muscle fatigue causes respiratory failure. To answer such questions, a series of experiments on human subjects has been initiated by Roussos and Macklem (238) and Roussos et al (239) who investigated the dynamic performance of the diaphragm at various levels of resistive respiratory work under normoxic and hypoxic conditions, in order to determine the time required to produce diaphragmatic fatigue. Pdi is known to represent the tension being

developed in the diaphragm (4), high Pdi indicates high load being sustained by the diaphragm. If the diaphragm sustains a fatiguing load, it will most likely fatigue. Resistive breathing, by itself, causes the efficiency of the respiratory muscles to be reduced in comparison to hyperventilation (195). Since efficiency is equivalent to work/energy consumed, it is reasonable to expect that if the rate of energy consumed was greater for the work being performed in comparison to that during unloaded hyperventilation efficiency will drop

Since the respiratory muscles are working less efficiently during resistive breathing than when hyperventilating (195) they are more likely to be predisposed to fatigue under such conditions. Increased airways resistance is a clinical condition which seems to occur more frequently than hyperventilation. For example, patients with chronic obstructive lung disease have a high airways resistance and may be predisposed to respiratory muscle fatigue. Thus, it is more important to test the influence of prolonged elevated airways resistance on the respiratory muscles than the influence of hyperventilation.

Roussos and Macklem (238) had demonstrated that at FRC when the diaphragm generages a pressure, with each inspiration of about 40% or more of maximum transdiaphragmatic pressure (Pdi max), it eventually becomes fatigued and the rate of fatigue was faster with higher loads, namely endurance time was less. However, if the diaphragm generated

less than 40% of maximum Pdi the load could be sustained indefinitely. Consequently, the 40% level was considered to be critical pressure (Pdi_{crit}). The load being sustained as percent of maximum as a function of time was demonstrated to have a curvilinear decay, similar to that described by Lieberman et al (179) on tension in relation to time, or by others relating MVV to time. These findings on the diaphragm are in agreement with data in the literature on other skeletal muscles; when the skeletal muscle contracts intermittently with contraction and relaxation time equal, it can continue to generate tensions of less than 40% of maximum without developing fatigue (15), sustaining higher loads which produce a shorter endurance time than when sustaining lower loads. It is also in agreement with Lieberman et al's findings (179) that 40% of the fibers in a guinea pig's diaphragm were of slow twitch - high oxidative type, which are hypothesized to be fatigue-resistant (46). In the study by Roussos and Macklem (238) and that of Roussos et al (239) it was found that recuitment of other inspiratory muscles to aid in producing the pressure influenced the onset of fatigue. When approaching the point of fatigue the subjects tended to produce a small Pdi and at that time abdominal pressure fell below its resting end expiration value, indicating strong recruitment of intercostal/accessory muscles in order to maintain ventilation. When all the inspiratory muscles were used to maintain the pressure the critical pressure was found to be 50-75% of the

maximum as opposed to 40% when the pressures were generated by the diaphragm only. They found that recruitment and derecruitment of the inspiratory intercostals and the diaphragm muscles, during resistive breathing delays the onset of fatigue. The level of critical pressure seems to be in good agreement with the 55% SHO and 45% fast twitch fibers composition reported by Liberman et al (179) in humans and by Keenset al (160) in rats.

The Factors Predisposing the Respiratory Muscles to Fatigue

Energetics: When the muscle contracts to exhaustion it may be considered as a system in which the equation of energy proposed by Monod and Scherrer (206) can be modified and applied to the respiratory muscles. This equation describes the relationship between the energy suplies, energy consumption and the development of fatigue.

$$C = W/E = \alpha + \beta t_{lim}$$

where: C = total energy consumed, W = total external work performed by the muscles; E = efficiency, α = energy stored in the muscle; β = rate of energy supplied to the muscle and t_{lim} = endurance time. These best measurable parameter is t_{lim} and it depends on all the other parameters in the equation. Thus, solving for t_{lim}:

$$t_{lim} = \frac{\alpha E}{W - \beta E}$$

where $\dot{W}$ = muslce power = W/t_{lim}.

From this equation it is clear that if $\beta E \geq \dot{W}$ the muscle could contract indefinitely without becoming fatigued. However, if $\beta E < W$ there will be a finite endurance time which would decrease with increase of load (power), a decrease in efficiency and a decrease in β or α, all of which would predispose the muscle to fatigue.

Roussos and Macklem (238) have utilized this model for the respiratory muscles and concluded that during resistive breathing when the diaphragm is the primary contracting muscle, the fact that fatigue occurs and that there is a finite endurance time indicates that energy demands exceed energy suplies. It might also indicate that despite Robertson's finding (230) in dogs breathing against resistive loads, that blood flow to the diaphragm increases exponentially without evidence of plateau, there is a limit to the capacity to increase diaphragmatic perfusion.

Hypoxia: Hypoxia would lead to a reduction in the rate of energy supplied to the diaphragm and this leads to a reduction in endurance time. When breathing against resistance under normoxic conditions $\overline{Pdi}_{crit}$ was found to be uneffected. However, hypoxia (13%O_2 in N_2) was observed to

have a significant effect on endurance time at levels above Pdi_{crit} and below maximum where the rate of energy supplied is important and the suppply of oxygen is critical (238).

These findings were different than those reported by Tenney and Reese (276) who found that breathing hypoxic mixture in 9 % O_2 in N_2 did not influence the endurance time in hyperventilation. These differences might be explained by McGregor and Becklake's findings (195) that resistive breathing produces a less efficient work by the respiratory muscles hence a greater requirement of oxygen. Consequently, in unloaded hyperventilation the respiratory muscles depend very little on anaerobic metabolism when normal lung resistance and compliance are maintained, even during hypoxia. However, during resistive breathing more anaerobic metabolism is necessary to meet the work demands. It is particularly significant under hypoxic conditions, in which oxygen supply to the respiratory muscles may be inadequate. This idea is supported by the results obtained by Eldridge (86) who demonstrated that breathing hypoxic mixtures against resistive loads leads to an increase in blood lactate whereas there was no increase in lactate during moderate hyperventilation in room air or 15% inspired oxygen, nor during normoxic resistive breathing. Eldridge's findings may also account for the difference between results on fatigue obtained by Roussos and Macklem (238) showing a difference in endurance time between normoxic and hypoxic resistive breathing and those obtained by Tenney and Reese (276) demonstrating no difference.

The Effect of Hyperinflation and Added Resistive Inspiratory Load on Respiratory Muscle Fatigue: Sharp et al (256) concluded from their study on patients with chronic airways obstruction that ineffectiveness or exhaustion of the inspiratory muscles working at a disadvantageously shorter initial length may play a major role in the development of hypercapnea and that failure of the respiratory muscles may be an important contributing factor in respiratory failure. There is experimental evidence that hyperinflation would not be possible without a substantial increase in muscle excitation (194).

In an isometric contraction the length of the muscle fiber is held constant, while in isotonic contraction the load is kept constant while the muscle is allowed either to shorten (miometric contraction) or to lengthen (pliometric contraction). Whether miometric or pliometric contraction occurs depends upon the size of the load. The force that can be generated at different muscle lengths, during a tetanus, under isometric conditions was demonstrated to be a function of the muscle fibers length (288). The maximum force can be developed when the muscle is approximately at its maximum unstretched length. In the respiratory muscles we cannot measure the force of the inspiratory muscles, we measure the pressure that the muscles can develop, which can be considered as an index of their force. Thus, the relationship between maximum inspiratory pressure and lung volume is an index of the force-length properties of the inspiratory muscles. If the muscle's initial length is shorter, the maximal force that can be developed will be reduced.

According to La Place $P \alpha \frac{2T}{r}$ where P = pressure, T = tension and r = radius of curvature. This implies that an increase in the radius of diaphragmatic curvature in hyperinflation would result in reduced initial diaphragmatic fiber length, hence reduce ability to generate the pressure. This inability to produce the necessary pressures and the inability of the diaphragmatic fibers to return to resting length would probably result in an increase of energy demand during inspiration per liter of ventilation, thus, predisposing the diaphragm to fatigue earlier.

Grassino et al (116) showed that for the same diaphragmatic myoelectric activity the generated Pdi was lower, at higher volume in comparison to FRC, indicating a need for greater energy consumption in generating the same pressure. Consequently, it is reasonable to hypothesize that fatigue of the inspiratory muscles would develop much more rapidly in patients with chest wall hyperinflation. Roussos et al (239) have shown that in normal subjects who actively maintain transpulmonary pressure at FRC +½ inspiratory capacity during resistive breathing, the critical mouth pressure was substantially reduced from a mean value of -80 cmH_2O at FRC to -27 cmH_2O at high lung volume. This represents a reduction of approximately 70%. The endurance time at each level of load was demonstrated to be significantly reduced at high lung volume in comparison with FRC breathing. These results point out that hyperinflation may be beneficial in opening obstructed airways and improving ventilation distribution

and gas exchange. Nevertheless, it does not seem to be beneficial to inspiratory muscle function, and it probably predisposes the inspiratory muscles to fatigue at much lower levels of resistive load.

Effect of Muscle Strength: With skeletal muscle contractions of less than 15% of maximum force an asymptote of almost infinite duration is observed. A second asymptote is approached between 70% and 100% of maximum effort when the contraction can be sustained for only a very short time. The shape of the curve is determined by the muscle blood flow (233). Impairement of blood flow is well recognized as a factor limiting endurance during isometric contraction. Little impairement occurs when the contraction force is less than 15% of maximum. Under such circumstances metabolism remains aerobic and there is no accumulation of acid metabolites (157,210,257). Between 15% and 70% of maximum effort, there is a progressively greater interruption of blood flow to the active muscles (157,210). Consequently lactic acid accumulates more rapidly and endurance diminishes. A strong muscle can produce a greater maximal force (expressed in kgm) than a weak one, a stronger muscle can sustain a greater force, without fatigue, than a weaker one. Thus a weak muscle may fatigue at a lower load than a strong one. An increase in strength should permit more forceful contraction without fatigue (258). Therefore weakness of the respiratory muscles should predispose to fatigue. In addition because of

the force-length relationship of the inspiratory muscles, the higher the lung volume the smaller would be the inspiratory pressure that could be developed by the inspiratory muscles for the same energy consumption (116,117), a condition which could amplify the effect of muscle weakness.

Situations where inspiratory muscle fatigue is a contributing factor: The current evidence suggests that respiratory muscles can become fatigued and that there are many situations where inspiratory muscle fatigue is likely to be a cause of respiratory failure. Although this still remains unproven there are most likely examples, such as respiratory infections in patients with neuromuscular weakness eg. quadriplegics. Saltin et al (240) demonstrated that after three weeks of bed rest VO_2 max was markedly reduced in both sedentary and well conditioned subjects. An increased stiffness of the rib cage has been observed in quadriplegic patients (29), patients with ankylosing spondylitis, and with scoliosis. This increased stiffness of the rib cage can lead to an increase in the work of breathing (29). Such an increase would most probably result in a higher energy demands which may not be met by the energy supplies, hence predisposing the muscles to fatigue. Therefore any patient who reduced his/her daily activity drastically, due to prolonged bed rest might be expected to show respiratory muscle weakness; and, breathing against an increased load, which could develop as a result of illness, most likely would result in fatigue and

perhaps failure. Patients who were ventilated for prolonged periods may have respiratory muscle atrophy and any increase of load such as when breathing on their own may predispose their inspiratory muscles to fatigue which may lead to failure.

The muscles known to atrophy most rapidly when put to rest are the ones we use the most. Certainly, the respiratory must be considered as muscles we use the most. Thus they atrophy, due to prolonger artificial ventilation. The maximum tension will diminish but any increased load presented by the lungs due to respiratory disease will remain. Thus, during the weaning period they may be able to breath quietly without distress for a short period, but then become progressively more dyspneic and arterial PCO_2 starts to climb. This inability to continue breathing without ventilatory assisance could be related to inspiratory muscle weakness and fatigue. Respiratory muscle weakness leads to inadequate ventilation and the resulting increase in arterial PCO_2.

There are probably many more situations in which respiratory muscle fatigue may play a critical role. In order to determine whether respiraotry muscle fatigue plays a clinically important role or not, a reliable means of diagnosing it is necessary.

Diagnosis of Fatigue in the Inspiratory Muscles: The ability to diagnose inspiratory muscle fatigue would have a considerable clinical value. In addition, it would be important that fatigue of the respiratory muscles be detected prior to the stage at which the muscles are unable to act as adequate force generators. The study by Roussos et al (239) revealed then when normal subjects breathe against fatiguing loads, at the mouth, they alternate between primarily using the diaphragm to predominantly using the intercostal and accessory muscles to develop the pressure necessary for ventilation. Such interaction may be considered as discoordination between the diaphragm and the intercostals and accessory muscles. Such asynchronous breathing has been previously reported by Ashutosh (12) and Sharp et al (255) who monitored the chest wall motion with magnatometers. In the light of the findings by Roussos and Macklem (238) and Roussos et al (239) this discoordination might be a sign of fatigue. This is yet to be demonstrated. It is possible that when breathing against a higher load the patients alternate between using one group of muscle to using the other in order to protect themselves against exhaustion.

A direct method of determining muscle fatigue using spectral analysis of the myoelectric signal is now available for other skeletal muscles. Thus, one of the goals reported in this thesis is to test whether this technique could be applied to the respiratory muscles.

Summary

The question whether the respiratory muscles ever become fatigued and play a significant role in respiratory failure was asked at the beginning of the century and has been frequently repeated. However, very few serious attempts have been made to document respiratory muscle fatigue. There have been a number of studies designed to determine the critical minute ventilation (MVV) that can be maintained indefinitely by normal subjects. The reported highest MVV that can be sustained indefinitely vary between 50% of maximum breathing capacity (MBC) and 80%. The reason for the discrepancy is not understood. Lieberman and co-workers (179,180) related the fiber composition of the diaphragm, in guinea pigs and rats, to the tension that could be sustained. In their studies no further decrease in tension was observed beyond 40% of maximum force, a value which corresponded with the observed 40% high oxidative slow twitch fibers. These studies indicate the respiratory muscle fatigue can be induced in animals. It was still necessary to determine whether respiratory muscle fatigue exists in human subjects and whether it plays a role in respiratory failure. Roussos and Macklem and Roussos et al (238,239) initiated a series of experiments in an attempt to answer such questions. It was revealed that when a normal subject is asked to breathe against fatiguing loads, using the diaphragm only, the critical Pdi is 40% of maximum.

This value is the same as reported for other skeletal muscles. However, if the subjects are asked to breath against fatiguing loads at the mouth, they alternate between predominately using the diaphragm to develop the necessary pressure, and using the intercostal/accessory muscles. This seems to delay fatigue which has been demonstrated by the increased level of critical pressure. In addition, Roussos and co-workers showed that fatigue occurs when the energy consumption of the inspiratory muscles exceeds the energy supplies. Furthermore they showed that hyperinflation and hypoxia coupled with resistive breathing predisposes the inspiratory muscles to early fatigue.

Respiratory muscle weakness and increased respiratory load can lead to inspiratory muscle fatigue. Such a condition may be frequent among quadriplegic patients who have a high mortality and morbidity rate due to respiratory complications. Disease also leads to reduced muscle strength and as a corrolary, increased strength results in the ability to sustain greater loads without undue fatigue. In order to determine whether respiratory muscle fatigue plays an important role, a reliable means of diagnosing it is necessary. Incoordination between the diaphragm and the intercostal/accessory muscles might be a sign of fatigue. However, a direct method of determining skeletal muscle fatigue has been developed. Spectral analysis of the myoelectric signal is available and we have attempted in the work reported in this thesis to apply this technique to the respiratory muscles.

II. 5 The Effect of Training on Skeletal Muscle Strength and Endurance

A person's potential for muscle strength and endurance is established at birth, since a given individual is born with a fixed number of muscle fibers (165). Muscle strength is a complicated property which has been defined as the tension that the muscle can exert in a single maximum contraction (61). A weak muscle has been shown to have a lower capacity for performance than a strong one (130,145,225, 258), and will also fatigue earlier. That is, it will have a lower endurance capacity (90). A well trained individual who exercises regularly is capable of greater strength and also a greater endurance. In other words, he/she will not only be able to generate a greater force but will also be able to work closer to his/her maximal strength or maximal oxygen uptake for longer periods of time (242,258). During training progressive changes take place in many physiological and biochemical aspects of the muscle and through these adaptations the ability of the muscle to work is improved. One of the objectives reported in this thesis was to train the respiratory muscles in quadriplegic patients primarily to improve endurance, but also to increase strength. Consequently, understanding what strength and endurance are and what changes occur in the muscle during the different training regimes is of fundamental significance in formulating a training program.

Strength: Muscular strength is characterized by the maximum tension that can be exerted and by the capacity of the muscle to recruit the maximum number of motor units in a given contraction (61). Gains in muscular strength can be achieved by exercising against a gradually increasing resistance (15,257). Gains in muscular strength are generally associated with muscular hypertropy (55) and muscular strengh has been shown to be proportional to the cross sectional area in an isolated muscle (193). However, often gains in strength are registered before there is measurable increase in dimension (97,272). The integrated EMG (IEMG) has been shown to be directly proportional to force (30,81,84). This linear relationship between force and IEMG is maintained after training (272). However the slope is more gradual (55,76,266). Chapman and Troup (55) have demonstrated that for a given level of load there was a significant fall in IEGM with increase of strength and the increased loads can be held with a decreasing number of motor units (272).

In addition, restriction of blood flow during isometric activity was found to be proportional to the intensity of contraction as percent of maximum voluntary force. With increased maximum strength a given load would constitute a smaller proportion of the maximum. Sustaining a load which is a small proportion of the maximum would demand less anaerobic energy. Thus, an increase in maximum strength should permit a more forceful contraction which might be sustained without fatigue (157,285).

Endurance: It is obvious that a gain in strength is important, however, gains in strength do not always mean a greater endurance there might even be a reduced isometric endurance (272). Since in the work presented in this thesis, endurance training was needed to improve the ability of the inspiratory muscles to sustain greater loads (such as might be imposed by acute respiratory infections) for longer periods of time, a more detailed review is given on endurance and the effect of endurance training on the physiological and biochemical adaptation that take place within the muscle.

Endurance training has been demonstrated to increase the level of force, as percent of maximum, that can be sustained for long periods (15,61). The critical load is the load below which fatigue is not observed and which can be sustained indefinitely. This load is 15% of maximum force for isometric contractions (206,258) and 40% for dynamic contractions when the duty cycle is such that the time of contraction equals that of relaxation (16,140). Training increases the critical level of load as shown by the fact that a well trained person can work indefinitely closer to his/her maximum capacity in comparison with an untrained person. Improved performance is achieved by adaptive responses that occur with training. Such skeletal muscle adaptations tend to optimize the muscle's ability to accomplish its increased functional demands. Such adaptation may include,

change in size (51,273) greater efficiency, greater metabolic capacity (90,113,135,138), increase in capillarization (242) and change in contractile properties (139,242).

The changes that occur with endurance training were demonstrated to be dependent on the type of training being imposed, isometric or dynamic endurance training, improving anaerobic or aerobic capacity respectively (112,151,278).

Principles of Training: Generally training entails exposing the muscle to a load or work stress of sufficient intensity, duration and frequency to produce a noticeable or measurable effect, ie. an improvement of function. To achieve this it is necessary for the intensity to increase as the performance improves since adaptation to a load takes place and the training load should be relative to the level of fitness of the individual (15,257). The need for a gradual increase in training load was demonstrated as early as 1931 by Christenssen (60). He evaluated the effect of training by measuring the heart rate, and observed that regular training with a given standard work load gradually lowered the heart rate. After training with higher work load, the original work load could be performed with still a lower heart rate. It appears that in fitness training for average people, a training load in excess of about 50 percent of the individual's maximum performance capacity (which is a level that would lead to fatigue) may be sufficient to produce a significant effect

(15). The training effect can be achieved by uninterrupted work or intermittent exercise (16). Physical activity ranging from repeated work periods of a few seconds duration up to hours of continuous work may impose a great load on the oxygen transport capacity and thereby induce a training effect, provided the work load is sufficiently high (16). It has already been pointed out that the effect of training is such that biochemical, neuromuscular, and circulatory changes take place which tend to change mechanical properties and the endurance capacity.

The Adaptations that Take Place with Endurance Training: Figure 3 shows a schematic, and in part hypothetical, summary of the adaptive responses with training (242). Maximal O_2 uptake may increase by 15-30% during the first 3 months of training and by 40-50% over the next 9-24 months. It has been shown in animal models and in human subjects that skeletal muscles, subjected to various forms of endurance training, develop an increase in oxidative capacity, mitochondrial enzymatic activity, mitochondrial number and fatty acid oxidation (90,112,138,139). Holloszy (112) clearly demonstrated that mitochondria are capable of adaptation and changes. The changes in the Krebs cycle which reflect oxidative capacity of the muscle fiber, and the respiratory chain enzymes are very important to the increase in the muscle functional capacity (112,135). As shown in Figure 3, during the first four weeks of training the difference between the increase in the oxidative enzymes and

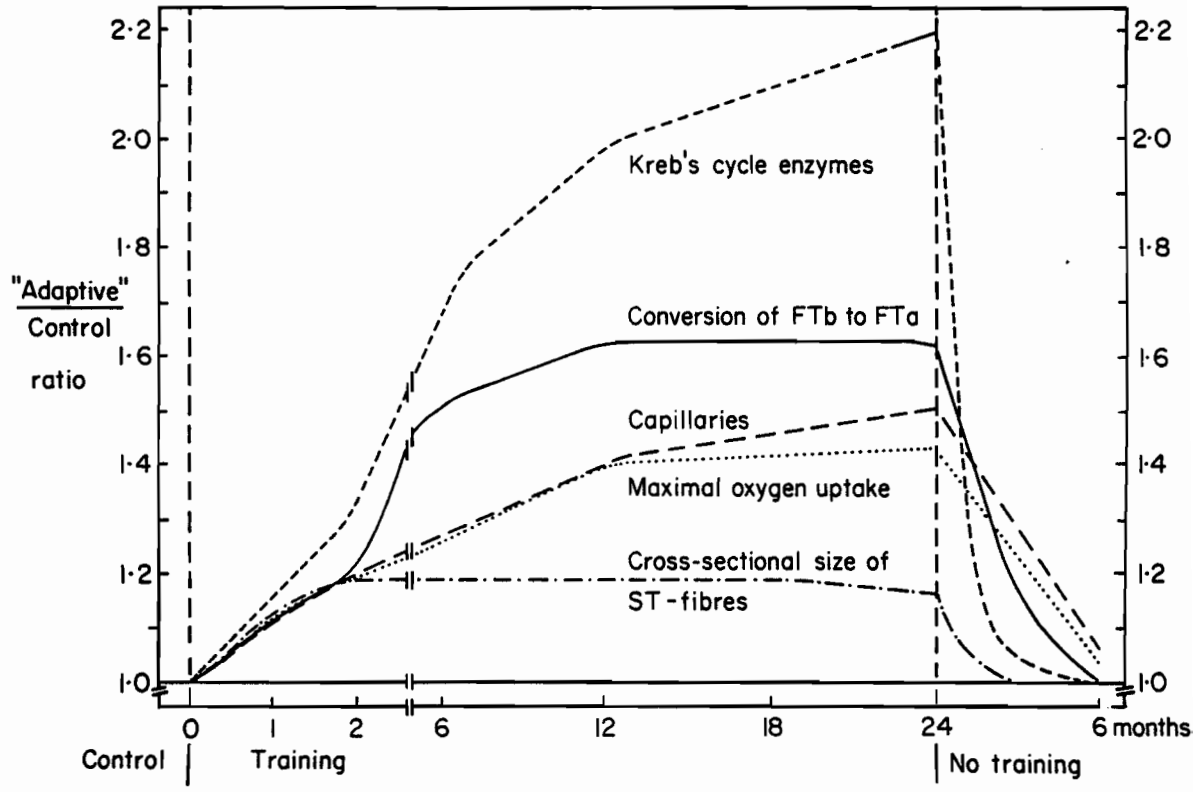

Figure 3: A schematic, and in part, hypothetical summary of some of the adaptations taking place in active muscle with endurance training (bicycling or running). (From Saltin et al, 242).

oxygen uptake was less than that observed after the first month (242). This might be due to the fact that oxygen uptake is not only related to the changes in oxidative enzymes but other factors such as blood flow, cardiac output are also important and could be limiting. Small changes in glycolytic capacity with endurance training were also observed (18). Despite an increase in the glycolytic capacity however, the trained muscle is less dependent upon glycolysis for energy production during moderate exercise (91) and it derives more energy from oxidation of fatty acids, indicating that a trained muscle has a higher efficiency and more economical energy utilization (15,242). Ianuzzo et al (144) demonstrated that the muscle DNA increased within the first few hours of being subjected to a chronic overload. However, most of the DNA increase was observed in the connective tissue rather than in the muscle fiber and its significance remains unknown (250). There are two main types of muscle fibers, slow twitch (ST) and fast twitch (FT). The fast type is subdividied into a type (FTa) (also FHO) which has higher oxidative capacity and b type (FTb) (also FLO) with lower oxidative capacity. Figure 3 also shows that endurance training increases the conversion of FTb to FTa type fibers (196). FTa fibers, which have a higher oxidative capacity have been found to be less fatiguable (44,46). The FTb which have lower oxidative capacity and contain less acto-myosin ATPase. Therefore, Saltin et al (242) claimed that such a conversion might be related to alteration in the acto-myosin molecules (44). A shift from fast to slow twitch type fibers as a result of training has

also been observed (144). In addition, it was demonstrated that in sedentary subjects the highest oxidative potential is in the slow twitch (ST) fibers whereas in highly trained individuals oxidative enzymatic activity of the FT fibers is as high as that in the ST fibers (285). Trained men deplete their muscle glycogen less rapidly than untrained ones during a standardized bout of submaximal exercise (244). In addition, trained muscles compensate for the smaller utilization of carbohydrate by oxidizing a proportionally greater amount of fat (242). This is reflected in a lower respiratory exchange ratio during the same exercise level in trained compared to untrained individuals (244).

An increase in maximum capacity of lactic acid (LA) production and utilization for energy has been demonstrated in many studies (9,245). In addition, the level of lactate during submaximal exercise was shown to be less in trained vs. untrained subjects (85,242). This is also supported by a reduced rate of utilization of glycogen in favour of fatty acid oxidation which results in a decrease in lactate (18,242). Since there is less lactate produced there is less change in pH. In addition, Brooke and Kaijser (44) demonstrated a reduced sensitivity to acid pH after some weeks of moderate endurance training (90). This may explain why the maximum capacity of LA could be increased. All the above metabolic factors are of primary importance in the enhanced work capacity, especially the capacity to perform intense exercise, for extended periods of time, with high aerobic demands.

As shown in Figure 3, and reported by others, capillary blood supply to a skeletal muscle can easily be increased and this increase is closely related to the level of activity of the muscles (9,39,242). The increase in capillary numbers is an important factor in improving oxygen delivery to the muscle. However, the reports regarding capillary density in men are conflicting. Saltin et al (240) did not observe significant increases in capillary density or number as a result of training. However Brodal et al (39) have demonstrated, using electron microscopy, that the mean number of capillaries in the vastus lateralis muscle was 41% higher in athletes than in nonathletes, and Andersen and Henriksson (9) demonstrated that training resulted in a 20% increase in capillary density. Similar results were observed in animals (242).

Effect of training on Fatigue: An increase in endurance postpones the development of fatigue (90). The development of fatigue is largely associated with an increase in lactic acid and increased sensitivity to low pH. A reduction of lactate production for a given work load and the reduced sensitivity to acid environment with training would be responsible for the delay in the onset of fatigue. A decrease in pH was shown to interfere with contractile function by increasing the calcium ion (Ca^{++}) binding capacity of the sarcoplasmic reticulum (90) and inhibiting the Ca^{++} binding to troponin (99). Phospho-

fructokinase activity is inhibited by a decrease in pH (90) resulting in feedback inhibition of glycolysis which in turn decreases ATP supply. Therefore, these mechanisms result in a decrease of contractile force. The increased acidity was shown to reduce conduction velocity of the neuromuscular action potential (185,210). In addition, Holloszy documented that training of the skeletal muscle has a protective effect against both lactate accumulation and the development of fatigue with exercise (138). It can therefore be concluded that muscles that have adapted to endurance exercise are more fatigue resistant than those that have not been trained.

The Effect of Training on EMG: The integrated EMG (IEMG) during maximal contraction in normal and atrophied skeletal muscle was shown to first increase and then decrease as a result of training (271). However, the initial increase in the myoelectrical activity was prolonged for six weeks in the atrophied muscle as compared to one week in normal muscle. Instead of observing the strength and endurance as separate entities, these investigators calculated the strength-endurance product. In the normal group the strength-endurance product reached a plateau after five weeks while the atrophied group showed a continued increase in the strength-endurance product. The decrease in electrical activity for a given level of load as a result of training could be correlated with a decrease in the syn-

chronously contracting motor units. Synchrony is considered less economical (273). In comparison, in atrophied muscle an increase in recruitment of synchronously contracting motor units was observed which contributed to the continuous increase in IEMG. This synchrony is less economical (203,204). In addition, progressive physical training of a specific skeletal muscle was shown to produce a gradual increase in the average duration of its potentials, and with a progressive diminution of their average frequency. Investigations with needle electrodes revealed that changes in the discharge frequency occured only at the beginning of training. Thus, the decline in the IEMG must be due mainly to asynchronization of simultaneously contracting motor units (271). In addition, it has been demonstrated that with training there is a progressive inhibition of the antagonistic muscles during the movement of flexion (24,223). Thus, in all probability the central nervous system is also affected by training, leading to improved coordination.

With fatigue an increase in IEMG and a shift from a high frequency to low frequency activity of the myoelectric signal is observed (153,182). Consequently, it is postulated that, with training the above changes observed in the EMG signal would disappear, indicating improved endurance.

Detraining: Forced inactivity of isolated limbs frequently results in a reduction of total body activity leading to general detraining of respiratory, circulatory, and muscular function. In a classical work Saltin et al (240) demonstrated that bed rest for a period of three weeks resulted in an average loss of 28% in maximum oxygen uptake, 11% reduction in heart volume, and 26% reduction in cardiac output, all have a severe debilitating effect.

Muscular inactivity results in a rapid loss in muscle mass and strength which can be observed within one or two days (114,212). Immobilization of a limb because of a cast results in a 22% loss of strength within the first 7 days, after which the loss is more gradual (212). A substantial decrease in oxidative enzymes after one week of inactivity, and a loss of 3 cm in circumference of the leg after 6 weeks of inactivity (114) was also shown.

As portrayed in Figure 3, after termination of training maximal oxygen uptake will slowly return to the pretraining level. On the other hand the concomitant changes in Krebs cycle and respiratory chain enzymes are much more rapid (242). Although less precise information is available regarding the time course for the magnitude of the conversion of FTb to FTa fibers and the degree of capillarization, the conversion of fibers was observed to decrease very rapidly as did the oxidative enzymes, while capillarization have a slow rate of decrease during detraining (see Figure 3). In summary, the skeletal muscles

are well adapted to training, however, this adaptation is reversed very rapidly if training stops.

Summary

Training can increase the maximal muscular strength up to its potential capacity and inactivity reduces it. Muscular endurance is the force as percent of maximum strength, which the muscle can sustain for prolonged periods of time. Training of the skeletal muscle produces adaptations which tend to optimize the muscle performance ie. accomplish its increased functional demands without undue fatigue.

Generally a skeletal muscle which is subjected to various forms of endurance training responds with increases in oxygen uptake, mitochondrial enzymes fatty acid oxidation and increase in capillarization, all of which are related to improvement in oxidative capacity. Small changes in glycolytic capacity have been observed. However, trained muscle is less dependent on glycolysis for energy production and more dependent on fatty acid oxidation. (Glycolysis is a less efficient and less economical source of energy.) Lactic acid production during submaximal exercise was demonstrated to be reduced with training. This, along with an increase in aerobic capacity postpones the onset of fatigue. In addition, a shift in fiber type towards a greater number of high oxidative fibers has also been observed as a result of increased endurance. These changes are also reflected in the myoelectrical activity that shows reduced IEMG with

training, and, for a given load the absence of the EMG fatigue signals, i.e. a shift in the spectrum from a high to low activity, is absent. These adaptations, however, may occur only if the muscle is exposed to exercise of sufficient intensity, duration and frequency. However, if training is stopped a rapid decrease in endurance capacity and a rapid disappearance of the adaptation that took place during training is observed (see Figure 3). Bed rest or weakening of the muscles to the point of atrophy was demonstrated to reduce muscle force, endurance and efficiency of contraction. In addition, it has been demonstrated that cessation of training would result in a rapid decrease in aerobic capacity as shown by a decrease in the capacity of oxidative enzymes, and the decrease in conversion from FTb to FTa type muscle fibers and a slower decrease in capillarization and oxygen uptake. Therefore, it can be concluded that because muscle endurance is correlated with resistance to fatigue, improving the muscle strength and endurance may be beneficial to patients with reduced muscle strength and endurance, while inactivity might be detrimental.

II.6 Training of the Respiratory System

Can the ventilatory muscles improve their strength and/or endurance in response to an appropriate specific respiratory muscle training program in the same way as other skeletal muscles? It has been demonstrated that ventilatory muscles, like other skeletal muscles can become fatigued (238,239). Respiratory muscle fatigue could contribute to respiratory failure which would be due to inadequate respiratory muscle power to overcome the respiratory load necessary for an adequate alveolar ventilation. If training of the respiratory muscles were to improve their strength and/or endurance it is reasonable to assume that the muscles could better withstand the imposed load and that they would be protected against the development of fatigue.

Breathing exercises have long been advocated as a remedial and therapeutic tool in patients who have respiratory insufficiency. Types of breathing exercises which have been most commonly advocated are: diaphragmatic breathing with an attempt to reduce the use of the accessory muscle activity (51,187); deep breathing, in order to open up poorly ventilated areas (1,51); breathing with prolonged expiration (27,51); pursed lips breathing to prolong the time of expiration (200,187,162,279); resistive breathing utilizing weights on the epigastric area in order to load the diaphragm (1). In addition, a technique such as application of vibration to the posterior chest wall to stimulate ventilation and gas mixing (20) was used. The benefit of all these exercises, however, is still controversial.

The first systematic study of the effect of breathing exercises in asthma was reported by Livingston and Gillespie (187). Such exercises in patients with respiratory insufficiency, particularly asthmatics, had been used as therapy for many years prior to Livingston and Gillespie. Previous studies were not systematically controlled, as opposed to this study, in which the investigators made regular check-ups on the patients including measurements of some lung functions at intervals throughout the treatment(187). They instructed their patients to breathe more with the abdomen in an attempt to improve the patient's control over the diaphragm. An improvement in 52 of the 75 cases in terms of severity and frequency of asthmatic episodes after one year of training was observed. The proportion of good results was comparable to that obtained from the control group who received specific medications but did not exercise. It was concluded that the breathing exercises were simple and produced equally good results as the more complicated program which involved taking medication. Miller (202) applied a similar program, of diaphragmatic breathing exercises, given regularly for a period of 6 to 8 weeks, to patients with chronic airways obstruction. He observed significant improvement in lung function such as tidal volume (VT) resting O_2 removal rate, VC, arterial PO_2 and diaphragmatic excursion; while decreases in breathing frequency and arterial PCO_2 were evident. Sinclair (267) however, did not observe changes in the value of maximal breathing capacity

in patients who underwent a 3 month training program directed at breathing more with the diaphragm and increasing the diaphragmatic excursion.

Campbell and Friend (51) who advocated diaphragmatic breathing and prolonged expiration, monitored the myoelectrical activity of the abdominal and accessory muscles. They also examined the ventilation during quiet breathing, during breathing with skeletal movement, during cough, and under rebreathing, and when instructed to use primarily their diaphragm, and to prolong expiration. These authors found no evidence that the breathing exercise training program affected the lung function and the breathing pattern. The effect of deep breathing on the poorly ventilated areas was tested and found to be negligible. Acute changes that occurred during breathing exercises in comparison with quiet breathing were reported to have no lasting effect (51). These changes were an increase in tidal volume and a decrease in FRC. The EMG activity portrayed an increase in the strength of the contraction of abdominal muscles during exercise compared with quiet breathing. It seems, however, that investigating the EMG activity of the inspiratory muscles such as the diaphragm and intercostals is more pertinent in determining the effect of breathing exercises.

Becklake et al (27) who performed lung function tests before and after breathing exercises also found no improvement in lung function despite some subjective benefits. They concluded that the subjective benefit expressed by the

patients arose from a subconscious desire to please those who treated them. However, it is possible that inappropriate methods of evaluation were employed.

Pursed lips breathing exercises were advocated in order to overcome dynamic collapse of the intraparenchymal conducting airways in patients with chronic respiratory obstruction (279). These investigators found improvement in respiratory rate, tidal volume and washout curves. Mueller et al, (200) who also tested the effect of pursed lips breathing exercise on ventilation and blood gases found similar lung function results to those described by Thomas et al, (279). They postulated that pursed lips breathing prevents airway collapse in patients with chronic airway obstruction; and, as a result, there would be less air trapping, an increase in tidal volume and a decrease in respiratory rate. However, further studies are needed to determine directly whether prevention of airway collapse is really benefical.

Breathing with progressive resistive exercise as advocated by Adkins was performed with weights applied to the epigastric area in patients with respiratory muscle paralysis. The aim was to provide resistance against which the diaphragm could contract. An improvement in the endurance was observed, namely the length of time the patients could breath against the load. No objective data was reported.

Barach and Dulfano (20) studied the effect of mechanical vibration applied to the posterior chest wall on pulmonary ventilation and on air mixing of patients with chronic obstructive lung disease. They observed the average minute ventilation of eleven patients to decrease from 8.8 to 7.4 l/min and an average decrease in frequency by 4.5 respirations per min. No improvement in the blood gases was observed. In fact the data suggested a less efficient gas exchange. It does not seem surprising that mere vibration did not produce any improvement in ventilation or in gas exchange.

Most of the breathing exercises described thus far were aimed at altering breathing patterns to affect lung function. Some of the methods related to patients with chronic lung obstruction, were designed to diminish air trapping and reduce the level of FRC. Although this may reduce the sensation of dyspnoea by lengthening the diaphragmatic fibers, thereby improving their mechanical efficiency and enabling the diaphragm to generate a greater force (194,221) for the same electric activation, the decrease in lung volume would lead to a decrease in the caliber of the airways. There would be a resultant increase in the airway resistance (79,284) producing airway closure, abnormal ventilation distribution and worsening of gas exchange. Conversely, lung function and gas exchange should improve by training the patient to breathe at a higher lung volume, but this would produce shortening of the inspiratory muscle fiber length , hence putting them at a mechanical disadvantage. Thus a paradox is presented.

Another objective of breathing exercises which have been described thus far, is alteration in the rate and depth of breathing. The rate and depth of breathing is under both automatic and voluntary control (216,227). To accomplish the above mentioned aim it would be necessary for voluntary alteration of the rate and depth of respiration to influence automatic control. Whether this occurs or not is at present unknown, but it would seem to be unlikely. Reliable evidence supporting the beneficial effect of breathing exercise in normal subjects and patients with respiratory insufficiency reported hereto, is either not available or some aspects are at best conflicting.

However, in a recent well controlled investigation, Leith and Bradley (177) opened up the field in a new and promising direction. They have demonstrated that specific ventilatory muscle training as opposed to breathing exercises significantly improved the strength and/or endurance of these muscles in normal subjects. In order to increase respiratory muscle strength subjects performed repeated inspiratory and expiratory maneuvers daily against obstructed airways. An increase of 55 percent in maximum inspiratory pressure was observed. The respiratory muscle endurance was defined as the highest level of ventilation that could be sustained for long periods. Thus, the endurance training program consisted of daily performance of voluntary normocapnic hyperpnea to exhaustion. Initially, all subjects could sustain hyperpnea at about 81% of their control 15 sec. maximum voluntary ventilation. This has increased to about 96

percent of maximum. The training effects were found to be specific to the training program.

In disease with respiratory insufficiency the ventilatory loads may increase and/or the capacity for sustaining them decrease. The role of ventilatory (respiratory) muscle performance as a limiting factor in the disability resulting from such diseases is largely unexplored and its importance in the development of, and recovery from, respiratory failure is not clear. Mechanical properties of the lungs may be the primary limiting factor in respiratory performance in patients with lung disease (62,178). However, the respiratory muscles can become fatigued (238,239) and if muscle endurance plays a role in performance it is reasonable to assume that improving the respiratory muscle endurance may be beneficial to patients with respiratory insufficiency. Keens et al (159) investigated the respiratory muscle endurance in patients with cystic fibrosis compared to normals. They also investigated the possibility of applying the training method used by Leith and Bradley (177) on these patients. In addition, Keens et al (159) tried to evaluate whether the same results could be obtained with a less specific training program than that proposed by Leith and Bradley. As expected, subjects with cystic fibrosis had lower maximum sustained ventilatory capacity than normal subjects, because they were breathing against a higher load. However, if the value of maximum sustained ventilatory capacity was corrected for FEV_1, the value for patients with cystic fibrosis,

were significantly higher than the values of normal subjects. Both the normal subjects and the patients showed a significant improvement in respiratory muscle endurance but the patients had twice the training response of normal subjects. A similar increase in respiratory muscle endurance was also observed in patients who trained with nonspecific physical activity. The improvement in endurance was not necessarily followed by improved lung function as measured by vital capacity (VC). In fact, in most patients or in normal subjects no change in VC was observed. In addition, once training stopped muscle endurance deterioriated. Thus, training must be continuous in order to maintain an increased level of ventilatory muscle endurance. The increase in endurance as a result of specific or nonspecific training programs may reflect adaptation within the muscles to stress of breathing against increased load.

Cellular Adaptation to Respiratory Muscle Training: It is well known that skeletal muscles respond to an increased functional demand by induced cellular adaptation, namely increases in oxidative capacity, mitochondrial enzymes and fatty acid oxidation (111,112,135,138,139). It is reasonable to ask whether the biochemical changes seen in the respiratory muscles correspond to those seen in other skeletal muscles when exposed to endurance training. It has been demonstrated that the guinea pig, rat and human diaphragms are composed of the same type of fibers as are other

skeletal muscles (160,179,180). Lieberman et al (179) showed the guinea pig diaphragm to have a fiber composition with 58% slow and fast twitch high oxidative fibers and 42% of the fibers were of low oxidative capacity. Human diaphragm was found to be composed of 55% high oxidative slow twitch fibers and 45% of fibers were fast twitch. Similar results were reported by Keens et al (160) in the rat diaphragm. They showed that 54% of the fibers are slow and fast twitch high oxidative type; while 45% are fast twitch low oxidative in type.

Lieberman et al (180) have demonstrated that treadmill running increased the fraction of high oxidative fibers in the guinea pig diaphragm, indicating an increase in the oxidative capacity. An increase in the oxidative capacity implies greater endurance capacity and greater resistance to fatigue (46,90,139). Keens et al (160) demonstrated that, in rats who were exposed to resistive breathing by banding the trachea, the diaphragm responded by shifting its contractile characteristics from fast twitch towards slow twitch in order achieve a more energetically efficient contraction. The importance of this adaptation is that the slow twitch myosin ATPase is approximately three times more efficient in sustaining an isometric contraction than fast twitch myosin ATPase (17). These changes occur only when the muscle is highly stressed (114). The internal intercostal muscles were shown to have histochemical changes with training, which is compatible with an increase in oxidative capacity, but

were not sufficiently stressed to induce change in myofibril ATPase (160). That is, there was an increase in the oxidative capacity of the intercostals but there was no change in the contractile properties.

In addition, Lieberman et al (179) correlated the histochemical fiber composition of the human diaphragm with the ability to sustain high levels of ventilation. They observed that the 5 minute hyperpnea could be correlated with the fraction of high oxidative fibers seen in the human diaphragm. They showed a curvilinear decrease in the level of MVV as a function of time, and implied that all fibers were recruited in maximal ventilation but the low oxidative fibers fatigued rapidly leaving the high oxidative fibers active by the end of 5 min. of exercise.

The diaphragmatic fiber composition correlates well with the findings that were shown by Roussos and Macklem (238) who showed that the diaphragm would fatigue if required to sustain loads greater than 40% of maximum transdiaphragmatic pressure. The response of the diaphragm to training, by an increase in oxidative capacity and the shift in the diaphragmatic fiber composition from fast twitch to slow twitch fibers, indicates that the diaphragm will also have greater resistance to fatigue because high oxidative fast twitch or slow twitch fibers have been demonstrated to have greater resistance to fatigue (91,114).

Cellular adaptation of ventilatory muscles to increased load has not been reported in man. There are some conflicting reports about the diaphragm in patients with chronic obstructive lung disease. Ishikawa and Hayes (148) found the diaphragm to be thicker in patients with chronic obstructive lung disease than in normals, reflecting hypertrophy. Steel and Heard (268) however observed reduced thickness in chronic bronchitics. They concluded that there was diaphragmatic atrophy because of decreased activity. Butler (47) showed the diaphragm size to be inversely proportional to the degree of emphysema. Keens et al (160) did not find hypertrophy in the rats' diaphragm. They suggested that respiratory muscle training produced intracellular adaptation instead of hypertrophy in response to increased loads. Under conditions such as hyperinflation where the diaphragm contribution to ventilation is decreased most of the respiratory muscle adaptation must occur in the intercostal accessory muscles (160). It is concluded that respiratory muscles do adapt to changing functional demands induced by increased respiratory load. Therefore, patients with an increased respiratory load who may be already trained but may not be able to withstand a further increase of load, and those with decreased muscle strength or endurance, should benefit from respiratory muscle training program.

Summary

Breathing exercises have long been advocated as a therapeutic tool in patients who have respiratory insufficiency. The types of breathing exercises are: diaphragmatic breathing, deep breathing, breathing with prolonged expiration, pursed lips breathing resistive breathing by putting weights on the abdomen, and applied vibrations to the posterior chest wall. All these methods were aimed at changing the breathing patterns thereby improving lung functions. The benefit of all these exercises is still controvertial. Since ventilatory muscles like other skeletal muscles can become fatigued and perhaps contribute to respiratory failure, training these muscles to improve their strength and/or endurance should be beneficial to patients with inadequate ventilation. Leith and Bradley (1976) opened up a new direction in the therapeutic approach provided by breathing exercises. They showed that specific respiratory muscle training improves the strength and /or endurance of these muscles in normal subjects. Keens et al (159) used the same respiratory muscle training method as proposed by Leith and Bradley. They corroborated the latters' results and demonstrated that ventilatory muscle endurance can readily be improved in normal subjects and patients with cystic fibrosis. They also demonstrated that both specific and nonspecific training improved respiratory muscle endurance. These changes take place because of cellular adapatation that occur within the muscle in response

to an increased load. Such adaptations have been shown to be: An increase in oxidative capacity, oxidative enzymes, increase in mitochondrial activity and number, an increase in the fatty acid oxidation, and perhaps a shift in contractile properties from fast twitch low oxidative fibers to slow twitch high oxidative fibers.

All this evidence points out that the endurance of the diaphragm can be improved by training thus enabling the patient to withstand an increase in imposed loads. Therefore, patients with reduced muscle power, such as quadriplegic patients, should benefit from a training program aimed at improving respiratory muscle strength and endurance.

II. 7 Respiratory Complications and Function in Quadriplegic Patients

Respiratory Complication: Traumatic injury to the cervical spine often results in spinal cord damage sufficient to produce permanent paralysis of the muscles innervated below the site of the lesion including most or all expiratory muscles and some of the inspiratory muscles. The prognosis for patients with such traumatic spinal cord lesions is influenced primarily by complications from the urogenital and respiratory systems. Most early deaths however are due to pulmonary complications (57,58,80,103,217,263). In recent years intensive respiratory care of these patients has reduced considerably the early and late mortality due to renal complications by a special training procedure (107,236). Despite improved intensive care, respiratory facilities and some reduction in the mortality rate due to respiratory failure, the death rate due to respiratory complications in the acute and late stages of trauma remains high (57,58,101,124,261). The acute stage is referred to as the first three months and it includes the period with spinal shock. The intercostal and abdominal muscles are paralyzed; and respiration is maintained almost entirely by the diaphragm or by external assistance, consequently, the ability to ventilate the lungs is reduced. The combined effect of the inability to produce forced expiration or cough, and the inability to inflate the

lungs fully because of muscle paralysis, sets the stage for retained secretions. The accumulation of bronchial secretions produces a constant threat of atelectasis and pneumonia. These were reported as the most common causes of respiratory failure in quadriplegic patients (28,37,287).

The rare cases of pulmonary emboli are usually fatal in patients with complete cervical lesions, in contrast to patients with either incomplete cervical or lower lesions. The size of the emboli may not differ but the patients with the complete cervical lesion have a very small vital capacity, particularly during the acute stage at which time vital capacity could be as small as 300 ml. Silver and Moulton (264) claimed that the pulmonary embolus in such a small amount of functioning lung tissue may reduce the volume by 50 percent and this would be immediately fatal. On the other hand, in patients with high incomplete and low level of lesions, "a similar pulmonary embolus may fall on a functioning lung tissue of approximately 1-3 liters and will still leave the patient with a viable reserve of function" (264). However, this explanation does not seem to be totally satisfactory. It seems more likely that patients with high and complete cervical lesions have less functioning inspiratory muscles in addition to a possible weaker diaphragm. Thus, the increased ventilation which normally results from pulmonary emboli would predispose the diaphragm to fatigue and might lead to respiratory failure. The dangers of a simple cold, or upper respiratory tract infection which could develop into a more complicated condition

are therefore great in the acute and late stages of traumatic injury and hence require preventative care. Most quadriplegic patients who survive the acute period are usually patients with lesions of the spinal cord at a level of the fourth cervical segment (CIV) or lower, which means that most or all of the diaphragm is innervated. Their prognosis is therefore better than in patients with very high cervical cord lesions who have no functioning diaphragm. Patients with a high level of lesion rarely survive, particularly when the lesion is a complete one (149).

Respiratory function in quadriplegic patients is altered because of the paralysis and the changes in the chest wall. These alterations constitute the greatest source of fatal complications, hence a detailed discussion on the effect of paralysis concerning the changes that occur in the respiratory system in quadriplegic patients is in order. The discussion will concentrate on the effect of the traumatic transection of the cervical spinal cord on a) the ventilatory functions such as respiratory forces, volumes and lung mechanics, and properties of the lungs; b) the chest wall movements; and c) neuromuscular activity and electromyography (EMG). In addition, the need for treatment will be evaluated and the effect of different treatment programs aimed at improving the respiratory capacity and lung function will be reviewed.

Subdivisions of Volume and Maximum Pressures: Quadriplegic patients are characterized by a marked reduction in the respiratory muscle force as reflected by reduction in maximum inspiratory and expiratory pressures; leading to a very marked decrease in total lung capacity (TLC), vital capacity (VC), inspiratory capacity (IC) and expiratory reserve volume (ERV), and to an increase in the residual volume (RV) (29,48,101,103,126,131,196). Reduced respiratory muscle force is an indication of respiratory muscle weakness. Due to paralysis of the expiratory muscles, a marked reduction in maximum expiratory pressure (Pe max) is observed which leads to a very marked decrease in ERV and an increase in RV (103). The expiratory reserve volume in some cases approaches a value of "O" (100,101,103,149).

It is generally agreed that the reduction in Pe max in patients with cervical cord lesions is due to the paralysis of the abdominal and expiratory intercostal muscles. Some of the observed interindividual variability in the Pe max might be explained by varying degrees of phasic or tonic activity in the intercostals and abdominal muscles (104, 262). Rhythmic activity of the intercostals has been observed in quadriplegic patients (125). Fugl-Meyer (104) tried to evaluate the influence of phasic activity in the intercostals by cooling the ribcage; because this activity

had been observed to be reduced by such a procedure (166, 197). Since Fugl-Meyer found no change in the expiratory force as a result of cooling they concluded that observed activity in the intercostal muscles did not influence the expiratory force (104).

In patients with cervical cord transection the maximum inspiratory force as measured by maximum inspiratory pressure (Pi max) is markedly reduced (28,101,131). The innervation of the main inspiratory muscle, the diaphragm, is probably not impaired in most patients with lesions below the CIV (131,205). Evidence of this was normal diaphragmatic excursions (48,101). The decrease in inspiratory force leads to a decrease in inspiratory capacity (IC) as well as a decrease in total lung capacity (TLC) (101,103). This reduction in IC and TLC can be attributed to both paralysis of the inspiratory intercostal muscles and weakness of the diaphragm. A distinction between the two factors could not be made. The explanation as proposed by Fugl Meyer (101) may be that in these patients PI max is measured at higher lung volume than in normals because of an increased RV. However, the reduced PI max might also be due to muscle weakness as suggested by Black and Hyatt (34). Stiffness of the rib cage (29,53) may be a contributing factor in the reduced volumes, especially in reduction of inspiratory capacity. The effect of rib cage stiffness on inspiratory force was demonstrated by Fugl-Meyer (104). He showed that after a cooling of the rib cage VC and expiratory reserve volume increased significantly ($P < 0.01$) and IC

increased only slightly. In addition, the RV was found to decrease. The mechanisms by which the cooling produced changes were described as follows: In traumatic quadriplegia normally spastic intercostal contractions occur and have been thought to contribute to better ventilation (125). This was contradicted by Fugl-Meyer (104), who claimed that cooling might reduce spasticity by reduced facilitation of spinal motor neurons and reduction in muscle spindle excitability (129,197). Consequently, reduced spasticity could be postulated to cause reduction in the rib cage stiffness hence allowing for greater lung inflation and better ventilation, as has been shown by the increased VC, ERV, IC and a decreased RV, but did not affect the respiratory forces.

The contradiction between the two studies may be interpreted as follows: Guttman and Silver claim that spasticity of intercostal muscles decreases the compliance of the rib cage and this resistance allows a more powerful diaphramatic contraction during the initial phase of inspiration (125). However, the spasticity is also restricting the expansion of the rib cage limiting the inflation of the lungs. Although the diaphragm develops greater tension, such tension will not result in greater inflation of the lungs. The increased diaphragmatic tension would likely increase the work of breathing predisposing the diaphragm to fatigue. Consequently the spasticity would not be advantageous to ventilatory function.

James et al (149) demonstrated a marked decrease in FRC in patients with high level cervical cord lesions which was consistant with stiffness of lung parenchyma. FRC represents an equilibrium between inward recoil of the lung and outward recoil of the relaxed chest wall (50). Since outward recoil of the relaxed chest wall is not thought to be significantly influenced by muscular paralysis (2) reduced FRC may be an indication for an increase in the lung recoil pressure. This theory could be supported by James et al (149) data demonstrating a reduced esophageal pressure (less negative) in high lesion quadriplegics. He concluded that these results reflected this decrease in lung complicance and an increase in static elastic recoil of the lungs. Thus, increased stiffness of the rib cage, and in some cases, a decrease in lung compliance caused by the paralysis of some of the respiratory muscles can be interpreted to predispose the respiratory muscles to fatigue and to a reduction in ventilation, which may lead to respiratory failure.

Alveolar Hypoventilation: In quadriplegic patients Bergofsky (20) found signs of alveolar hypoventilation which resulted in an increase in retension of PCO_2. He believed that this was caused by increased work of breathing due to altered chest wall mechanics. However, this increase in PCO_2 with normal lungs indicates respiratory muscle weakness which does not enable the patient to withstand the increased work of breathing. His findings were supported by Haas et

al (126) who demonstrated that the quadriplegic patients required approximately 4.2 cm H_2O of pleural pressure to inspire less than 600 ml whereas a normal individual required only 2.3 cm H_2O of pressure for a breath of 600 ml. Consequently, the compliance of the lung in quadriplegic patients was demonstrated to be lower than in normal subjects ie. 120 ml per cm H_2O compared with 200 ml per cm H_2O in the normal subjects. Therefore the work of breathing in quadriplegic patients is much greater than in normal subjects. Alveolar hypoventilation was also demonstrated in at least 2 of the subjects in the study of Haas et al (126). McKinly et al (196) could not support this data. Silver (261) found that quadriplegic patients could not increase their ventilation above 32 litres per minute due to the paralysis of their respiratory muscles. In addition he reported that at these levels the oxygen consumption was 1.6 ml per litre excess of ventilation. This was slightly but not significantly higher than the reported values for normal subjects (52) but lower than in patients with cardiopulmonary disease. However, in quiet breathing the oxygen consumption was not above 230 ml per minute. It was therefore concluded that the oxygen consumption of the respiratory muscles was not excessive. James et al (149) clearly demonstrated CO_2 retention indicating alveolar hypoventilation in patients with high levels of cervical spinal lesion. The discrepancy between studies could be explained by the fact that McKinly et al (196) tested patients with lower

levels of spinal transection than those described by Bergofsky (29), by Haas et al (126) and James et al (149). Normal blood gases were demonstrated in patients with low levels of lesion as compared with high levels of lesion (126). Respiratory muscle inability to produce sufficient ventilation because of the increased work of breathing could be the cause of the resultant alveolar hypoventilation.

Chest wall Movement: In animal experiments a decrease in the rib cage movements has been shown after cervical cord transection (68). Duchenne (77) has already observed that the rib cage moved paradoxically with inspiration in patients with flaccid paralyis of the intercostals. Recent studies have demonstrated that some paradoxical movements of the rib cage also occur in patients with spastic quadriplegia (211,262,264). Bergofsky (29) and Kelts et al (161) did not observe respiratory movements of the chest wall in quadriplegic patients, while others demonstrated the rib cage movements to be different from those of normal subjects (102,196) and to some extent paradoxical, which means indrawing of the rib cage during inspiration. Despite the fact that the principles outlined by Konno and Mead (171) were followed in these experiments, a discrepancy in the results was apparent. The discrepancy could be attributed to the different methods used ie. different positions of magnetic coils.

Neuromuscular Activity: The activity of the respiratory muscles, specifically that of the intercostals and the abdominal muscles in normals has been a subject of research for many years. However, the literature on electromyographic studies of the respiratory muscles following transection of the cervical cord is minimal. In 1963 Grossiord et al (122) studied the action of the shoulder girdle and abdominal muscles during breathing in a group of quadriplegic patients, using a combination of spirometry and electromyography. They observed that the shoulder girdle muscles were contracting during expiration. Guttman and Silver (125) showed that once the stage of spinal shock had subsided, they could observe EMG activity recorded from the intercostals which was synchronous with inspiration. They interpreted the observed EMG in the intercostal muscles to be an indication of the development of reflex activity similar to that produced by stimulation of the plantar reflex.

Silver and Abdel-Halim (262) have found the observable rhythmic EMG activity of the intercostal muscles increase with increasing inspiratory volumes. They also explained that the observed EMG activity in the intercostal muscles is due to the development of a stretch reflex. Quadriplegic patients with transection below the fourth cervical spinal segment were shown to have normal diaphragmatic activity (48,122) as assessed by normal diaphragmatic excursion. This is consistent with the origin of innervation to the diaphragm, namely from the third, fourth and fifth cervical

segments. However, it seems surprising that the diaphragmatic EMG was not investigated in quadriplegic patients in whom, theoretically, the EMG recording should present no technical difficulties.

Summary

The mortality rate from respiratory failure among patients with a traumatic injury of the cervical spine is still high despite improved care. The prognosis of these patients is most influenced by complications from the respiratory system. The primary causes of respiratory complications are acute pulmonary edema, atelectasis, pneumonia and in some cases pulmonary emboli.

The etiology of the respiratory complications in these patients may be as follows: The injury produces paralysis of respiratory muscles innervated from spinal segments below the level of the lesion, this leads mainly to spastic paralysis. The spastic paralysis causes reduced respiratory forces reflected by a reduction in inspiratory and expiratory pressures. Reduced inspiratory force results in a reduction in vital capacity, total lung capacity and inspiratory capacity. The impaired expiratory muscle function reduces expiratory pressure which results in a reduction of expiratory reserve volume virtually to zero and also leads to an increase in residual volume. The properties of the chest wall were demonstrated to change because of the

paralysis; for example, the stiffening of the rib cage which reduces rib cage compliance. Reduced rib cage compliance was shown to lead to increase in the work of breathing. It was also reported that patients with high levels of cervical lesions develop alveolar hypoventilation which is believed to be caused by the increased work of breathing because of the altered chest wall mechanics and the paralysis. However, there is no general agreement regarding the existance of alveolar hypoventilation in quadriplegics. In addition, the oxygen cost of breathing in these patients has not been demonstrated to be excessive. The discrepancy between these studies seems to be due to the types of patients being studied.

A paradoxical movement of the chest wall in quadriplegic patients has been demonstrated by several investigators. It has been primarily attributed to reduced rib cage compliance and the lack of abdominal resistance provided to the diaphragm. Despite the paralysis and minimal observed movement of the rib cage, electromyographic activity was observed in the intercostal muscles. The observed EMG was attributed to the development of reflex activity. However, it is surprising that no evidence was found regarding EMG activity of the diaphragm, which is known to be intact in most quadriplegic patients.

The immobility of the patient and perhaps prolonged use of external ventilatory assistance could produce muscle weakness in the innervated respiratory musculature. This being the case it is reasonable to assume that a specific respiratory muscle training could be beneficial to these patients.

II. 8 Treatment of the Impaired Respiratory Function In Quadriplegic Patients

When the quadriplegic patient is free of respiratory infection, respiratory function is rarely a problem unless the level of lesion is above the fourth cervical segment. However, respiratory function and ventilatory capacity become a critical matter when the patient has an acute respiratory infection. Increased secretions are poorly cleared due to the paralysis of expiratory muscles, and the work of breathing might be elevated by such infections, due to increased airways resistance (100,149), and this may lead to respiratory failure.

In quadriplegic patients decreased maximum inspiratory and expiratory pressures are well documented (28,101,103, 126). This reduction in respiratory forces indicates respiratory muscle weakness to which is added increased ventilatory loads. Subdivisions of lung volumes and rib cage mobility are altered by respiratory muscle paralysis and weakness (see II.6.2). Historically, respiratory impairment in quadriplegic patients has been accepted as permanent and irreversible. Long term studies of the respiratory functions of patients with cervical cord lesions show that such respiratory impairment deteriorates if not treated (29, 126). Present-day rehabilitation methods no longer permit the severely paralyzed patient to remain in bed but demand his active participation in an active program. Such

participation demands increased ventilation. Consequently, ventilatory capacity which may be sufficient for immobility or minimal activity may not be adequate to meet increased metabolic demands. For effective rehabilitation to be realized treatment programs developed to improve ventilatory function. Studies evaluating such programs in the last two decades are very few and the existing ones concentrated on maintenance of rib cage mobility and increasing respiratory muscle strength. Assisted cough in quadriplegic patients requires them to inflate the lungs after which the therapist applies a sudden push against the abdomen thereby producing a positive pressure. A larger lung volume prior to the procedure, would allow for greater positive pressure to be produced as a consequence of the sudden motion performed on the patient (260). Consequently, improvement of ventilatory functions is important particularly because the efficiency of assisted cough was demonstrated to be directly proportional to the vital capacity and the elastic properties of the lungs. Cough is an important factor in sputum transport from the airways to the mouth, hence preventing its accumulation in the airways.

Glossopharyngeal breathing (GPB) is one technique of breathing exercise used in the rehabilitation of quadriplegic patients. It is a substitute method of breathing (2,69,199). By using the muscles of the mouth, tongue, soft palate, and throat, the patient with respiratory muscle paralysis or weakness

can force air into the lungs. The GPB was first used by patients with respiratory muscle paralysis caused by poliomyelitis (2,69,70) since the 50's GPB has been included as part of the rehabilitation exercises for traumatic quadriplegic patient. Metcalf (199) found that after GPB training 23 quadriplegic patients could increase their vital capacity from 60 percent to 81 percent of normals. Montero et al (208) and Adkins (1) demonstrated similar results. In addition, Montero et al (208) observed an increased duration of breath holding by 63 percent; maximum breathing capacity increased from 35 to 65 percent of normal and expiratory flow increased from 39 to 92 percent of normal. There were no changes in the ERV, timed VC, breathing frequency or tidal volume. Such large changes are yet to be confirmed and before they are accepted a more detailed description of the testing procedures are necessary. These authors also reported an improvement in endurance capacity (1,208). They claimed that improving endurance with glossopharyngeal breathing requires considerable learning time and close supervision. It is not clear at all how simple inflation by forcing some air into the lungs which does not affect inspiratory musculature directly, would improve endurance. This makes it impractical for general application. Adkins (1) used several other techniques in his treatment program to improve the breathing ability in children with respiratory muscle paralysis. He evaluated respiratory muscle strength by testing the patients' vital capacity. Respiratory muscle endurance was assessed by the duration of spontaneous breathing off ventilatory support. Adkins'

treatment started with re-education in the use and control of the diaphragmatic motion. Then, once the patient could control diaphragmatic motion, diaphragm strengthening exercises were added to the program. Gradually increased weights were applied to the epigastric area. An increase in respiratory endurance as well as strength resulted. However, no objective data was reported. Fugl-Meyer (100) investigated increased mobility of the chest wall and respiratory muscle strength in quadriplegic patients. Total lung capacity was measured initially, and a volume of 25 to 100 percent of the difference between the predicted and the measured TLC was then insufflated, using a pump. This maneuver was repeated 10 times. Subsequently, patients were required to forcefully expire through a resistance at the end of each of the next 10 insufflations. The latter maneuver was aimed at increasing respiratory muscle strength. The treatment resulted in an increase in TLC, ERV, VC maximum voluntary ventilation, as well as maximum inspiratory and expiratory pressures. In addition, it was demonstrated that the dynamic lung compliance, which was shown to be frequency dependent before treatment, became almost independent on breathing frequency in three patients. The reported changes are impressive, however, the increase in ERV could only be explained if the patients have some innervated expiratory muscles or possibly recruited other muscles than those known as expiratory muscles and this was not elaborated. Insufflation may indeed prevent some chest wall stiffness thus ventilation may be improved. Cheshire (57) used

an incentive spirometric technique to increase lung volumes, and also observed improvement. However, neither the study by Fugl-Meyer (100) nor that by Cheshire (57) deal with the problem of impaired respiratory muscle endurance. As previously mentioned, the ability of quadriplegic patients to withstand augmented metabolic demands for any length of time is dependent upon endurance.

SUMMARY

Impaired ventilatory capacity and respiratory function due to respiratory muscle weakness has become critical when quadriplegic patients have to meet augmented metabolic demands. Historically such impairment has been accepted as permanent and irreversible. Since it has been demonstrated that ventilatory force and function would deteriorate if not treated, rehabilitation programs for quadriplegic patients in the last two decades included breathing exercies. Very few studies however, assessed the value of such programs. The type of exercises that have been evaluated were glossopharyngeal breathing, restrictive breathing (by applying weights to the epigastric area), ventilatory insufflation and incentive spirometry. All these were aimed at maintaining rib cage mobility and improving respiratory volumes and forces. Most reports did not have either a detailed description of the techniques or else no objective data was presented.

Treatment was demonstrated to result in increases in TLC, VC, ERV, and respiratory pressures. The most convincing treatment seems to be insufflation of the lung. There is no available information regarding respiratory muscle endurance although endurance is known to be correlated with resistance to fatigue and with improved ability to withstand augmented metabolic demands. Consequently, the study reported in this thesis concentrates on evaluating a respiratory muscle endurance program as a therapeutic technique for such patients.

CHAPTER III

EXPERIMENTS

EXPERIMENTS

III.1 The EMG Pattern of Diaphragmatic Fatigue

a. Summary

We studied the effect of breathing at various levels of transdiaphragmatic pressure (Pdi) on the EMG power spectrum of the diaphragm. The diaphragmatic EMG was measured simultaneously with a bipolar esophageal electrode (EE) and surface electrode (SE) placed on the ventral portion of the 6th and 7th intercostal spaces in 5 normal subjects breathing at FRC against an inspiratory resistance. During each fatigue run the subjects generated a Pdi, with each inspiration, that was 25, 50 or 75 percent of maximum Pdi (Pdi_{max}) for a period up to 15 minutes. During runs at 50% and 75% of the Pdi_{max}, which are known to produce fatigue, we found for both EE and SE a progressive increase in the amplitude of the low frequency (L = 20.0-46.7 Hz) and a decrease in the high frequency (H = 150-350 Hz) component of the EMG. These changes were not seen at 25% of Pdi_{max}. The diaphragmatic H/L ratio was independent of Pdi when the diaphragm was not fatigued. H/L fell while the diaphragm performed fatiguing work and this was more rapid at higher Pdi's. It was therefore concluded that frequency spectrum analysis of the EMG can detect diaphragmatic fatigue reliably, prior to the time when the diaphragm fails as a pressure generator.

b. Introduction

In order to determine if respiratory muscle fatigue ever causes respiratory failure it is necessary to develop a method by which respiratory muscle fatigue may be diagnosed clinically. Skeletal muscle fatigue has been defined as the inability to maintain a predetermined load (266). Based on this definition Roussos and Macklem (238) defined diaphragmatic fatigue as the point at which an inability to sustain a predetermined level of transdiaphragmatic pressure was observed. This method of detecting diaphragmatic fatigue, in fact, measures the point of muscle exhaustion and does not provide information on the time course of muscle fatigue. Furthermore, it requires gastric and esophageal pressure measurements and is thus not really applicable to sick patients. It has been shown that fatigue can be detected before exhaustion, in skeletal muscles other than the diaphragm, by observing the changes in the frequency spectrum of the myoelectric potentials (153,154,168,183). These studies of skeletal muscle fatigue have revealed that when a fatiguing load is sustained by the muscle, the amplitude of the high frequency component of the EMG decreases exponentially with time and the amplitude of the low frequency component, and the total integrated signal gradually increases (153,154,168,247). We have applied this technique to the diaphragm in order to explore its usefulness as a diagnostic test. In this paper we report the effect of breathing at various levels of transdiaphragmatic pressure on the relative amplitudes of low and high frequency components of the diaphragmatic EMG.

c. Methods and Procedures

Five normal subjects were studied. All experiments were performed with the subject seated in a Faraday cage. Transdiaphragmatic pressure (Pdi) was measured as the difference between gastric pressure and esophageal pressure, and used as an index of the mechanical tension produced by the diaphragm (110). These pressures were measured by means of two thin walled latex balloons, 5 cm long, connected to a catheter (PE 200, 75 cm long) one positioned in the stomach and the other in the middle third of the esophagus (Figure 1). The catheters were connected to the two ports of a differential transducer (Sanborn 267B) to measure Pdi. Esophageal and gastric pressures were also measured relative to atmospheric pressure using two additional transducers (Sanbord 267B) to estimate pleural and abdominal pressures respectively. We also measured the electrical activity (EMG) of the diaphragm by esophageal (EE) and surface skin electrodes (SE).

The esophageal electrode consisted of a double lumen catheter (Swan-Ganz). An inflatable latex balloon was attached at the distal end of one of the catheters (116). Four insulated copper wires ran inside the lumen of the other catheter, each of them ended in a 2 mm wide, 2 mm thick silver ring. The rings were 6 mm apart and the EMG was recorded from the most distal rings that were 18 mm apart. To position the electrode the distal end was passed through the nose into the stomach where the balloon was

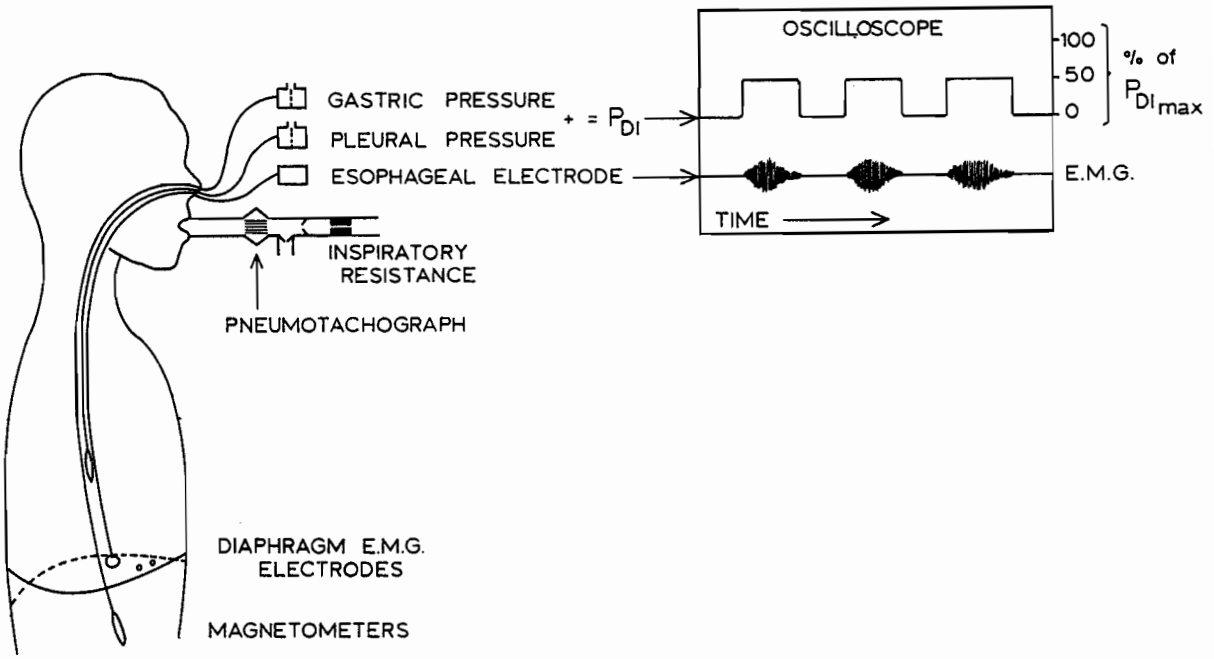

Figure 1: Diagrammatic representation of the experimental design. Subjects inspired through resistance in order to be able to produce the predetermined transdiaphragmatic pressure (Pdi). Pdi was measured with two balloons as the difference between gastric and esophageal pressure, and was displayed on the oscilloscope. EMG of the diaphragm was measured by surface electrodes (SE) and esophageal electrode (EE).

inflated with 10 cc of air. The other end of the catheter was allowed to hang free and moved in and out with each breath. The electrode measured the EMG activity from the crural portion of the diaphragm as described by Grassino et al (116). An external pair of bipolar silver chloride skin electrodes (Beckman 255-083547-A) with 8 mm diameter discs were placed one electrode on the sixth and the other on the seventh intercostal spaces 1 cm from the costal margin of the rib cage, at approximately right angles to the direction of the fibers of the abdominal oblique muscles. These electrodes were secured to the skin by means of double adhesive tape rings. Interelectrode conductivity was improved by adding saline gel between the electrodes and the skin. The interelectrode resistance was kept below 10 K ohms. This bipolar pair of EMG electrodes recorded the myoelectric activity from the costal portion of the diaphragm. We were concerned that the external skin electrodes might pick up EMG activity from the abdominal muscles and that the EMG pattern of diaphragmatic fatigue recorded by these electrodes might be masked by the abdominal muscle activity. To test this, another pair of bipolar surface electrodes were placed on the abdominal surface at the level of the umbilicus. Our reasoning was that if the SE showed EMG changes with fatigue similar to those of the EE whereas the abdominal electrodes did not, we would assume that the abdominal activity did not interfere significantly with the recording of the diaphragmatic EMG pattern of fatigue.

The EMG recording and analysis: The myoelectric potentials were picked up by two pairs of bipolar electrodes and conditioned by a Hewlett Packard 8811A differential amplifier with band-pass filters of 10-1000 Hz. The signal from the preamplifier was recorded simultaneously on magnetic tape for further analysis (Hewlett Packard tape recorder model 3960) and strip chart paper (Hewlett Packard strip chart recorder model 7758A). The signal from the tape was subsequently passed through two band-pass filters with ranges of 20.0 to 46.7 Hz for the lower frequency component (L), and 150 to 350 Hz for the high frequency component (H)[1].

The band-pass filters are of similar frequency range to those used by Kadefors et al (125) on the biceps. The filtered signals together with the unfiltered input (Tot) were rectified, integrated through a leaky integrator (time constant 0.1 sec), and recorded on strip chart paper. (See Figure 2).

Experimental Procedures: Diaphragmatic fatigue was produced by inspiring through a resistive load varying from 50-200 cm H_2O/l/sec. The subject developed a Pdi with each inspiration that was a predetermined fraction of the maximum Pdi that the subject could develop at FRC (238). In order to estimate the maximum, the subjects made a maximum inspiratory effort, at FRC, against an occluded airway prior to the fatigue run. The resultant Pdi was assumed to be the maximum that could be developed at FRC. Subsequently, the subjects breathed through resistances connected to the

[1] This equipment was built by W.R.D. Ross, Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada.

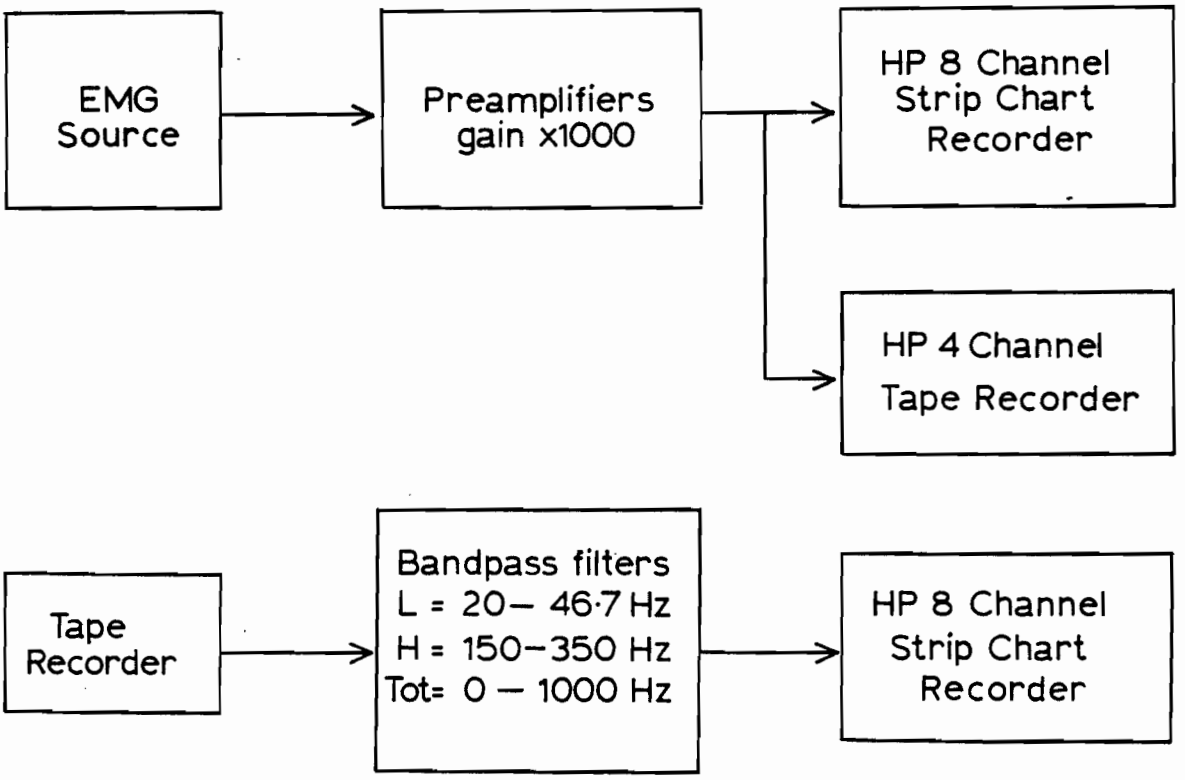

Figure 2: Schematic representation of the EMG signal recording and processing.

inspiratory inlet of a Hans-Rudolf valve. Expiration was unloaded. The mouth flow was in the range of 0.2 to 0.3 l/sec. Pdi was displayed on an oscilloscope and each subject was instructed to develop the predetermined Pdi throughout inspiration and to continue to breathe in this manner as long as possible or until told to stop. The Pdi's chosen were 25%, 50%, or 75% of their maximum. Each subject chose his own rate and depth of breathing and the presentation of loads was randomized. At 75% Pdi max the runs lasted for 2 to 3 minutes, whereas for 50% and 25% Pdi max they lasted 10-15 minutes. Respiratory rates varied between 8 and 12/min. In order to allow for complete recovery from fatigue, subjects rested for 30 minutes between tests. End tidal PCO_2 was monitored throughout, using a CO_2 meter (Godart Capnograph). Data at 25% Pdi max was obtained in only 4 subjects.

EMG Data Analysis: Figure 3 presents the tracings obtained during three breaths in one of the subjects. Prominent electrocardiographic signals are seen in the rectified integrated tracings of the low frequency components and of the total EMG. These signals lasted approximately 0.4 sec and had to be manually gated to ensure that the electrocardiogram was not contributing to the low frequency power of the EMG. Thus measurements were done during diastole when the ECG contributed very little to the measured signal.

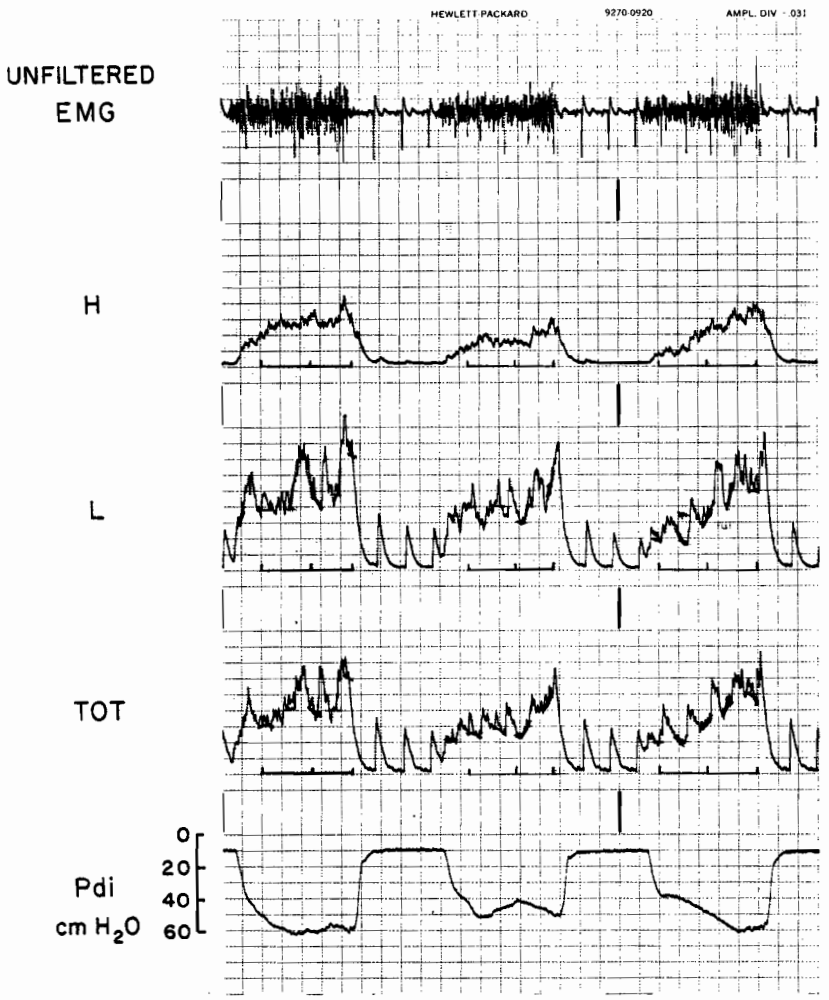

Figure 3: Example of raw data obtained in one subject during three breaths. H and L are the amplitudes in arbitrary units of the high (150-350 Hz) and low (20-47.7 Hz) frequency components respectively of the filtered diaphragmatic EMG shown in the top panel. TOT is the total amplitude. Pdi is transdiaphragmatic pressure. The marks on the baseline of H, L and TOT indicate the three points during inspiration when measurements were made. Paper speed 10 cm/sec. The recording was made by SE.

We measured the amplitude of the H and L signals in arbitrary units and calculated their ratio (H/L). Measurements were made at the beginning, middle and end of each breath at a time when Pdi was relatively constant. Three consecutive breaths were analyzed and the mean value of the 9 measurements of H/L ratio was taken to give a single value for this time span. There was considerable variability in individual H/L ratio measurements, both within and between breaths as shown in Table 1, which gives the values for the amplitudes of the high and low frequency components of the diaphragmatic EMG, and their ratio for the 9 measurements made on the breaths in Figure 3. The decrease in H/L ratio with time was used to describe the EMG pattern of fatigue in a manner similar to that used by others for different skeletal muscles (153,168). The regression lines for H/L ratios, slopes and intercepts for each run were calculated.

d. Results

As shown in Figure 4, there was no systematic relationship between the H/L frequency ratio of the diaphragmatic EMG and transdiaphragmatic pressure ($r = 0.09$) when the muscle was nonfatigued. This was true for all subjects. The nonfatigue H/L ratio varied between 0.43 and 0.90. Similar results were reported by Kogi and Hakamada (168) for the biceps brachii. We therefore concluded that the nonfatigue diaphragmatic H/L frequency ratios were independent of load. However, variation of H/L ratio from day to day

TABLE I

High and Low Frequency Amplitudes and Amplitude Ratios of Diaphragmatic EMG shown in Figure 1

		Phases of Inspiration		
Breath #		Early	Middle	Late
1	H+	7	18	17
	L+	20	35	30
	H/L	0.35	0.51	0.57
2	H	10	16	16
	L	17	27	32
	H/L	0.59	0.59	0.50
3	H	6	14	19
	L	17	19	29
	H/L	0.35	0.74	0.66

+ Amplitudes of high (H) and low (L) frequency components of EMG expressed in arbitrary units.

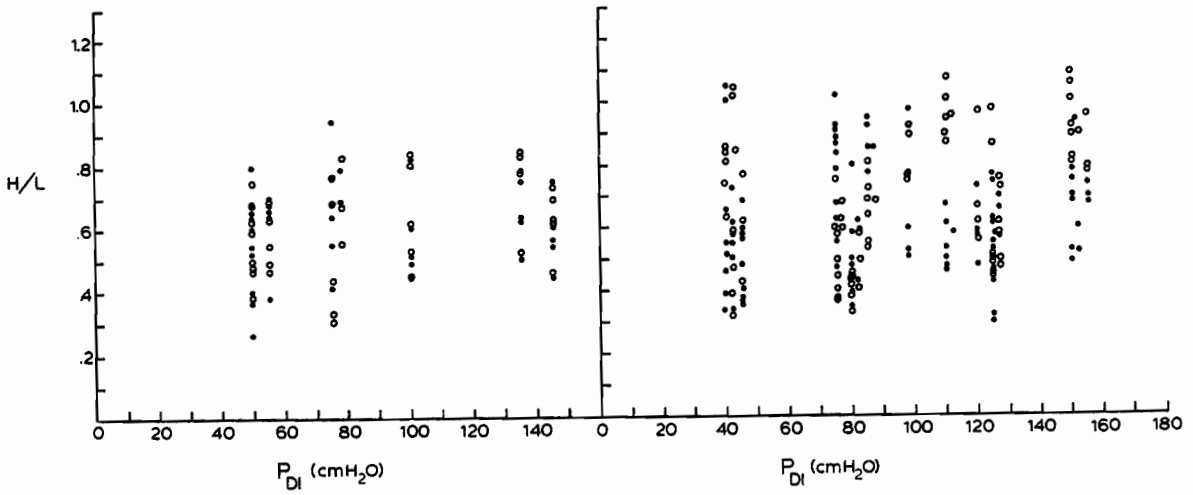

Figure 4: The relation between H/L ratio of the diaphragm, in nonfatiguing contraction, and Pdi for a single subject (left panel) and all subjects (right panel). ● esophageal electrode, o surface electrodes (correlation was not significant).

within the same subjects was large. For this reason we took the H/L ratios of the first three breaths of each run, averaged them and designated this value as 100%. The H/L ratios of all subsequent breaths were referred to as a percentage of this value.

There was a tendency in 3 subjects for the H/L ratio to fall during the course of inspiration when the diaphragm was not contracting against a fatiguing load (25% Pdi max). In the other subject, in whom measurements were made at 25% Pdi max, there was no discernable change. In no subject was the change statistically significant, and mean values for the four subjects combined showed no significant change throughout the breath.

The changes in the H/L ratio with time during inspiratory resistive loading in one subject are shown in Figure 5A, and mean values for all subjects are shown in Figure 5B. No systematic change in the H/L ratio occurred while breathing with a Pdi of 25% Pdi_{max} which is insufficient to produce fatigue (193). At fatiguing loads of 50% and 75% of Pdi_{max} there was a systematic decrease in the H/L ratio after the first few breaths. The slopes of the regression lines for the ratio changes in the fatiguing runs were found to be significantly different from those of nonfatigue runs which had zero slopes (Table II). Furthermore, with higher fatiguing loads (75% Pdi_{max}) the slope was steeper than with the lower fatiguing loads (50% Pdi_{max}).

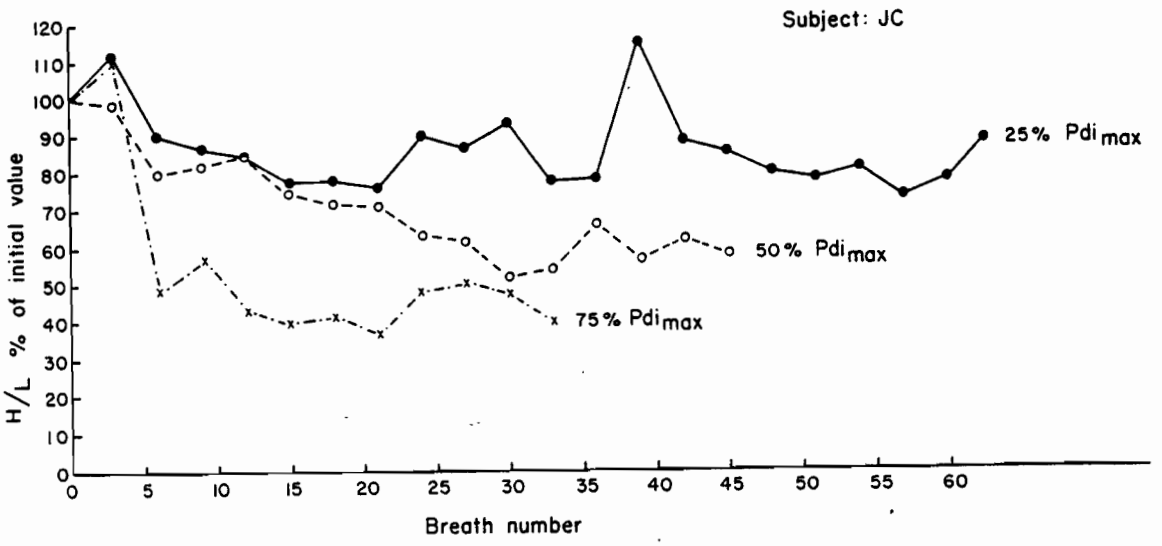

Figure 5: **A)** Changes in H/L ratio of the diaphragm as a function of time (breath number) for the different values of Pdi in one subject. Data were obtained with the surface skin electrodes. Each point is the average of 3 inspirations.

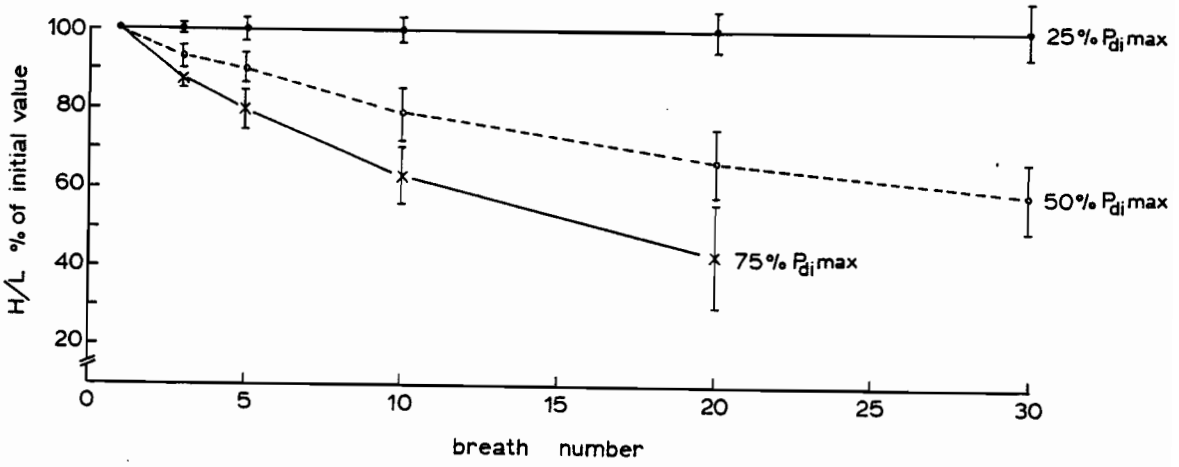

Figure 5: B) Mean values ± 1 SE of H/L ratio plotted as a function of breath number for all subjects. Data were obtained with the surface skin electrodes.

TABLE II

Mean Slopes of Regression of H/L Ratio vs Breath Number

	%Pdi_{max}	25	50	75
SE	Slope	0.001	-0.108	-0.20
	r	0.37	0.93	0.96
EE	Slope	0.0001	-0.190	-0.271
	r	0.02	0.96	0.98

SE = Skin electrode; EE = esophageal electrode

r = exponential correlation coefficient

The rate of reduction in the H/L ratio with time was found to be steeper for records obtained from the esophageal electrodes (EE) compared to skin electrodes (SE) (Figure 6). Furthermore, it is shown in this figure that while there was a fall in the H/L ratio detected by the surface electrodes in 6th and 7th intercostal spaces, no such changes were observed or records obtained with the abdominal electrodes.

e. Discussion

Roussos and Macklem showed that when the diaphragm generates a pressure with each breath of about 40% or more of Pdi_{max} and the end tidal level is at FRC, diaphragmatic fatigue results (238). They estimated that transdiaphragmatic pressures of less than 40% of Pdi_{max} could be developed with each inspiration more or less indefinitely.

These authors defined fatigue as the inability to maintain a predetermined Pdi. If diagnosis of respiratory muscle fatigue is clinically important in patients, ideally this should be made before the muscles are no longer able to sustain the load necessary for adequate ventilation. EMG techniques which accomplish this by reliable and noninvasive means which show a change in the power spectra of the EMG signal are now available for other skeletal muscles (153,168,183). This change is detected by a decrease in the amplitude of the high frequency activity of the myopotentials and an increase in amplitude of the low frequency activity. Our results show the same shift from H to L

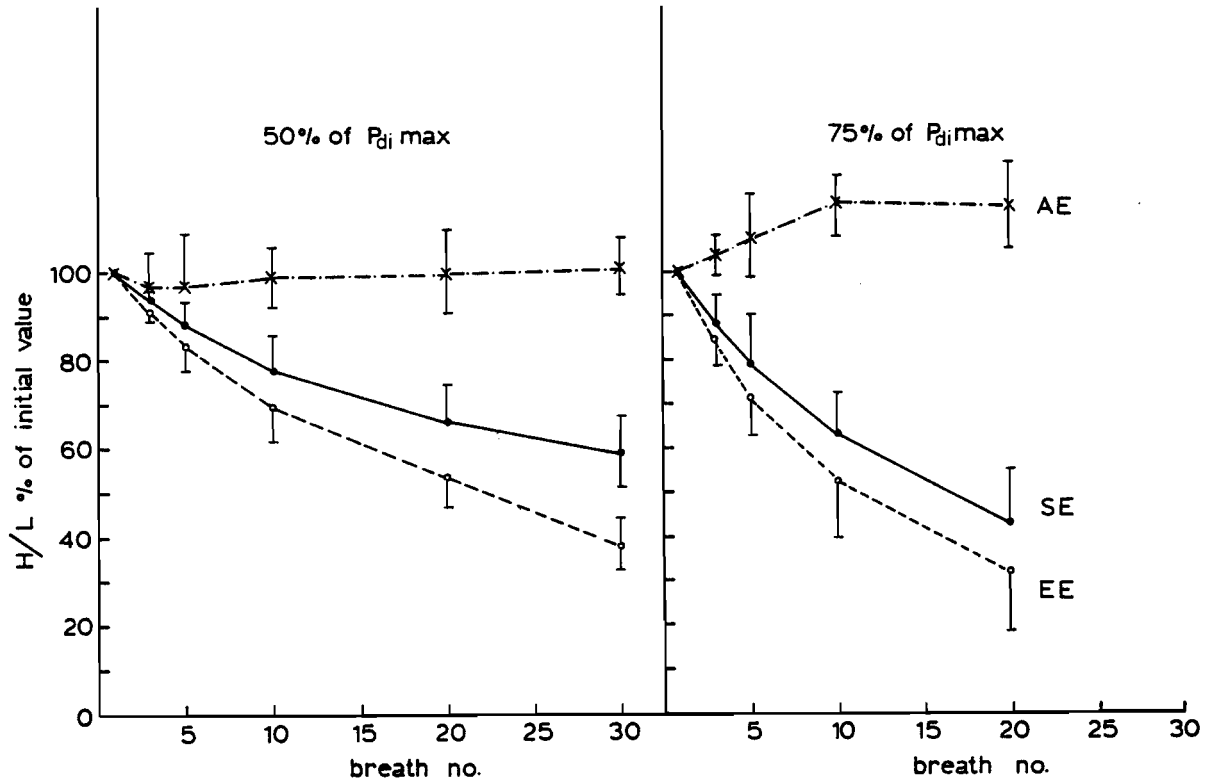

Figure 6: Mean values of H/L ratio of the diaphragm for all subjects as a function of breath number; recording simultaneously with the esophageal electrode, EE (●-----●), and skin electrodes, SE (o——o). The H/L ratio of the abdominal muscles was recorded with surface electrode, AE, (x-.-.x) . The left panel shows the data at 50% of the right at 75% of Pdi(max). Bars indicate ±1 SEM.

activity when the diaphragm sustains fatiguing loads as witnessed by the reduction in the H/L ratio. Furthermore, this fatigue was detected by skin electrodes.

The selection of bandwidths to analyze, of 20.0-46.7 and 150-350 Hz was based on the data for other skeletal muscles (153,185) which show that the major change in the EMG power spectrum with the development of fatigue, occurred in these bands. Additional factors in the choice of the low frequency bandwidths were, the desirability to remove any noise due to motion artefacts in which most of the frequency content is less than 10 Hz, and to avoid interference from 60 Hz waves. In order to avoid 120 Hz interference the low frequency cutoff for the high frequency bandwidth was chosen to be 150 Hz. The bandwidth for each frequency range was the same when measured in octaves. There was a longer range of frequency in the higher bandwidth because the total power over this frequency range is small and needed to be maximized in order to improve signal/noise ratio. Although, ideally it would have been preferable to measure the whole frequency spectrum of the diaphragmatic EMG, we lacked the equipment to make this analysis. As a second choice we selected the H/L ratio as the index of fatigue that we wished to investigate because it had already been shown to be useful for skeletal muscles.

Before accepting the fall in H/L ratio as indicating fatigue one must be certain that electrocardiographic artefacts are not influencing this signal. As shown in Figure 3

most of the interference from the electrocardiogram appears in the 20.0-46.7 Hz filter. Thus, it may contribute substantially to the low frequency amplitude if appropriate steps are not taken to gate it. This we did manually as described earlier. Nevertheless, if the ECG amplitude is very much larger than the low frequency EMG amplitude one may have to gate the signal over a period of time of several integrator time constants in order to avoid electrocardiographic contamination of the EMG. A situation might conceivably arise, when the heart rate is sufficiently rapid and the ECG amplitude is sufficiently large in comparison to the EMG amplitude, where it is impossible to gate the ECG using a 'leaky' integrator. This would lead to an underestimate of H/L ratio. This potential source of error could lead to a progressive fall in H/L ratio with time if there were a systematic increase in heart rate during a run. For all data reported in this paper, there was no change in heart rate between the beginning and end of the runs, which were of relatively short duration. We, therefore, conclude that the progressive fall in H/L ratio at 50% and 75% Pdi_{max} that we observed was not due to ECG artefact.

The shift in the EMG power spectrum during fatiguing contractions was postulated by Lindstrom to be due to a reduction in neuromuscular conduction velocity (183). This reduction is primarily attributable to an inadequate blood flow to the contracting muscle in relation to its power output which results in the accumulation of waste products

such as lactic acid (210). If this is so then the fatigue that we produced in the diaphragm is presumably related to an energy demand by the diaphragm which is greater than the energy supply.

Kogi and Hakamada (168) measured the ratio of the low frequency to the high frequency components of the EMG recorded from the biceps brachii, and showed that in non-fatiguing contractions it was not dependent upon the force developed by the muscle. We found similar results for the diaphragm in that there was no correlation between H/L ratios and Pdi, when Pdi is the parameter the tension of the diaphragm (110). We feel therefore, that a progressive decrease in H/L is a relatively specific predictor of diaphragmatic fatigue and is independent of changes in diaphragmatic tension.

We have shown that when sustaining fatiguing loads the slope of the diaphragmatic H/L is greatest within the first 10-15 breaths and tends to plateau thereafter. Kadefors et al (153) observed an exponential decrease in H/L and Kogi and Hakamada (168) found similar changes.

Lieberman et al produced fatigue of the guinea pig diaphragm (179). They found that with the development of fatigue, there was an exponential decay in the maximum tension that the diaphragm developed, reaching an asymptomatic value of about 40% of maximum in about 10 minutes. They found that 40% of the diaphragm's fibers were slow twitch, rapidly oxygenating, red fibers, which, it is postulated,

resist fatigue (174). This would account for their observation, and those on humans (238) that the diaphragm could maintain a tension of 40% of maximum more or less indefinitely. For other skeletal muscles, Thorestensen and Karlsson (278) found that muscles with a higher proportion of fast twitch, slow oxidative, white fibers fatigued faster than muscles with a higher proportion of red fibers. Thus, the rate of change of diaphragmatic H/L may be related to the type of muscle fibers that comprise the diaphragm and the rate at which they fatigue.

Our results indicate that when the diaphragm was sustaining greater loads, the fall in H/L ratio was steeper. This is similar to the data of Kogi and Hakamada (168) for the biceps brachii muscle. Gollnick et al (91) have shown that with higher loads there is preferential recruitment of fast twitch fibers and thus greater susceptability to fatigue. This may account for the steeper H/L curves during stronger diaphragmatic contractions.

The changes in H/L ratio detected by skin electrodes were comparable to those of the esophageal electrode as shown in Figure 6. However, the slopes for the esophageal electrode were steeper than those for skin electrodes. This difference could be due to several factors. The skin electrodes are facing the costal portion of the diaphragm while the esophageal electrodes are facing its crural portion. Thus, the two sets of electrodes might be recording electrical activity from different fibers or different motor units

and consequently showing different rates of change in H/L with time.

Even if the skin electrodes record activity from the same motor units they definitely have a different geometric relationship with respect to the contracting fibers than the esophageal electrode. Lindström in 1973 (183) has clearly demonstrated that the distance between electrodes, the distance from the source fibers to the electrodes and other geometrical variables are important factors in the power spectrum. Therefore, variations in the geometry of electrodes relative to the contacting fibers may lead to differences in the frequency spectrum, as measured by esophageal and skin electrodes.

The esophageal electrode is made of a different material and located in a different tissue environment than the skin electrode. Thus there will be different dielectric properties for both types of electrodes and the dielectric properties have an influence on the frequency spectrum (183).

In addition, although the electrical activity of the abdominal muscles does not prevent detection of the falling H/L ratio from the skin electrodes, it may be included in the total signal these electrodes develop. If this is so, and if the abdominal H/L does not change with time, one would predict a greater decline in the H/L for the esophageal electrodes which presumably detect no abdominal activity.

In spite of these differences between esophageal and skin electrodes it appears that the skin electrodes are able to detect myoelectric signals of diaphragmatic fatigue satisfactorily and reliably. Because this method is non-invasive and provides evidence of fatigue before exhaustion, it may prove particularly useful in establishing a diagnosis of respiratory muscle fatigue in patients.

III.2 The EMG Pattern of Inspiratory Muscle Fatigue

a. Summary

The effect of breathing at various levels of mouth pressure (Pm) on the EMG frequency spectrum of the diaphragm and intercostals (IC) was studied in 4 normal subjects. The EMG was measured with bipolar surface electrodes placed on the ventral portion of the 6th and 7th intercostal spaces and on the parasternal region of the 2nd and 3rd intercostal spaces, for the diaphragm and intercostals respectively. During each breathing test the subjects generated, with each inspiration, a Pm which was 25, 50 or 75 percent of their maximum Pm (Pm_{max}) for a period of 3 to 10 minutes. Inspiratory flow and end tidal Pco_2 remained constant. During runs of 25% of Pm_{max} no change in the H/L ratio was observed. When the load increased to 50 percent, the EMG pattern of fatigue was observed, for either the diaphragm, or the intercostals, or both, depending which group of muscles was primarily active. However when sustaining a load of 75% of maximum we found a progressive decrease in the H/L ratio for both muscles. In addition, it was observed that when the muscle activity stops, allowing for recovery to occur, the H/L ratio rapidly returns to pre-fatigue value. Frequency spectrum analysis, specifically, the change in the H/L frequency ratios can therefore detect fatigue of the inspiratory muscles prior to the time of mechanical failure. It was also demonstrated that the inter-

costals and diaphragm could fatigue independently and that recruitment and derecruitment of the two sets of muscles occur.

b. Introduction

In a previous communication (121) we showed that diaphragmatic fatigue can be detected before exhaustion by measuring a shift in the power spectrum of the surface EMG towards lower frequencies (121,153,183). This shift in the frequency spectrum was evident by a reduction in the ratio of the amplitudes of the high frequency (H) to low frequency (L) components (H/L) (121). No change in the H/L ratio was observed during non-fatiguing work, whereas during fatiguing work the H/L ratio decreased progressively.

This was a controlled experiment in the sense that the pressure developed by the diaphragm (transdiaphragmatic pressure; Pdi) was constant from breath to breath. However, if EMG spectral analysis is to be useful in detecting inspiratory muscle fatigue clinically, then it needs to be shown that the H/L ratio provides evidence of fatigue when the pressures developed by the inspiratory muscles varies from breath to breath. This is particularly so, as experiments producing fatigue of the inspiratory muscles showed that there was a cyclic recruitment and derecruitment of intercostal muscles and diaphragm.

The purpose of this study was to describe the EMG pattern of inspiratory muscle fatigue during resistive breath-

ing when the pressures developed by the inspiratory muscles were allowed to vary from breath to breath.

c. Methods and Procedures.

We studied four normal subjects, 3 males and 1 female, ranging in age between 32 and 40 years. The subjects were seated in a Faraday cage throughout the experiments.

Mouth pressure (Pm) was measured by a catheter attached to a mouth piece on one side and to a pressure transducer (Sanborn 267B) on the other. Pdi was measured as the difference between the gastric pressure (Pab) and the esophageal pressure (Pes), and used as the index of tension produced by the diaphragm (110). Pab and Pes were also measured relative to atmospheric pressure in order to estimate abdominal and pleural pressures respectively. This was necessary in order to determine which group of muscles (intercostals or diaphragm) primarily contributed to ventilation during resistive breathing. These pressures were measured using the same technique as previously described (Chapter III.1, Methods). We measured flow rate with a pneumotachograph (Fleisch No. 3) and a differential pressure transducer (Validyne MP 45-2). The flow signal was integrated to measure changes in volume. We also sampled expired gas at the mouth throughout the experiments and measured the concentration of CO_2 with a CO_2 meter (Godart Copnagraph).

A pair of bipolar skin electrodes (Beckman 255-083547-A) with 8 mm diameter discs were placed on the sixth and seventh

intercostal spaces, 1 cm from the costal margin of the rib cage as described in Chapter III (Methods). This pair of bipolar electrodes recorded the EMG activity from the costal portion of the diaphragm. A second pair of bipolar skin electrodes was placed on the second and third intercostal spaces for men, and on the first and second spaces for women, one centimeter parasternally. These electrodes recorded the myoelectric activity of the inspiratory intercostal muscles. The myoelectric activity and the mouth pressure were recorded on a four channel tape recorder (HP Instrumentation recorder 3960). The pressures volume and flow were all recorded on an 8 channel strip chart recorder (HP Model 7758A).

The EMG Recording and Analysis: The myoelectric activity of the intercostals and diaphragm was conditioned, processed and filtered by a Hewlett Packard (8811A) differential amplifier with a band pass filter of 10-1000Hz. The signal was recorded on a tape recorder and then passed through high frequency and low frequency band pass filters after which it was rectified and integrated. The integrated signal was recorded on a strip chart paper and analyzed with a digitizer, in order to measure the average amplitude of the high and low frequency components of the EMG signal and calculate the ratio H/L for each inspiration. All the data was expressed as mean values of H/L ratio for every three breaths in percent of initial value. The details of this technique have been previously described (Chapter III.1. Methods).

Experimental Procedures: Prior to each experiment the subject performed a maximum inspiratory effort for 2-3 seconds at FRC with the inspiratory line occluded. This maneuver was performed several times in order to obtain the maximum inspiratory pressure (Pm_{max}) that the subjects could generate at FRC. Pm_{max} was found to be between 100-130 cmH_2O for all subjects. Subsequently, the subjects were instructed to breathe through an inspiratory resistance, connected to the inspiratory inlet of a Hans-Rudolph valve with expiration unloaded. The flow was found to be in the range of 0.3-0.5 l/sec. The subjects were instructed to generate a constant Pm, with each inspiration, which was a predetermined fraction of Pm_{max}. Pm was displayed to the subjects on an oscilloscope to assist them with this task. The subjects were instructed to continue to breathe in this manner as long as possible or until told to stop. We were not interested in measuring endurance time (t_{lim}) (239). We selected loads of 25,50 and 75% of Pm_{max}. From previous experiments we knew that the lightest load was non-fatiguing while the heaviest produced fatigue. Subjects chose their own tidal volume and frequency of breathing and were not given any instructions regarding how they had to develop the target Pm. The subjects were therefore, free to use their diaphragm, or intercostal/accessory muscles, or both in order to generate the desired Pm. In order to allow for complete recovery from fatigue subjects rested for 30 minutes between tests.

d. Results

The changes in the H/L ratio with time during inspiratory resistive breathing in 4 subjects who maintained loads at 25, 50 and 75% of Pm_{max}, are shown in Figure 1A and B. When sustaining a load of 25% of Pm_{max} (left hand panels), substantial interbreath fluctuations in the value of the H/L ratio (expressed as percent of initial value) were observed. However, the overall slope ramained approximately zero for both the diaphragm and the intercostal muscles. When a load of 50 percent of Pm_{max} (middle panels) was maintained a reduction in the H/L ratio was observed in either the diaphragm, or the intercostals or both, depending on which muscle was predominantly active. The values of gastric pressures were used as an index, of which muscle was primarily used in generating the pressure, and are shown in Figure 2. In this figure the gastric pressure developed during the runs in which loads of 50% of maximum were sustained. When a low Pg was developed during the resistive breathing run the EMG pattern reflecting the development of fatigue was observed in the recording made from the intercostals and not from the diaphragm. Conversely, when a high Pg was developed the EMG pattern of diaphragmatic fatigue was observed. At fatiguing loads of 75% of Pm_{max}, (right hand panel of Figures 1A and 1B) a progressive decrease in the H/L ratio for both, the diaphragm and the intercostal muscles, was observed after the first few inspirations. In most cases the rate of reduction in the H/L

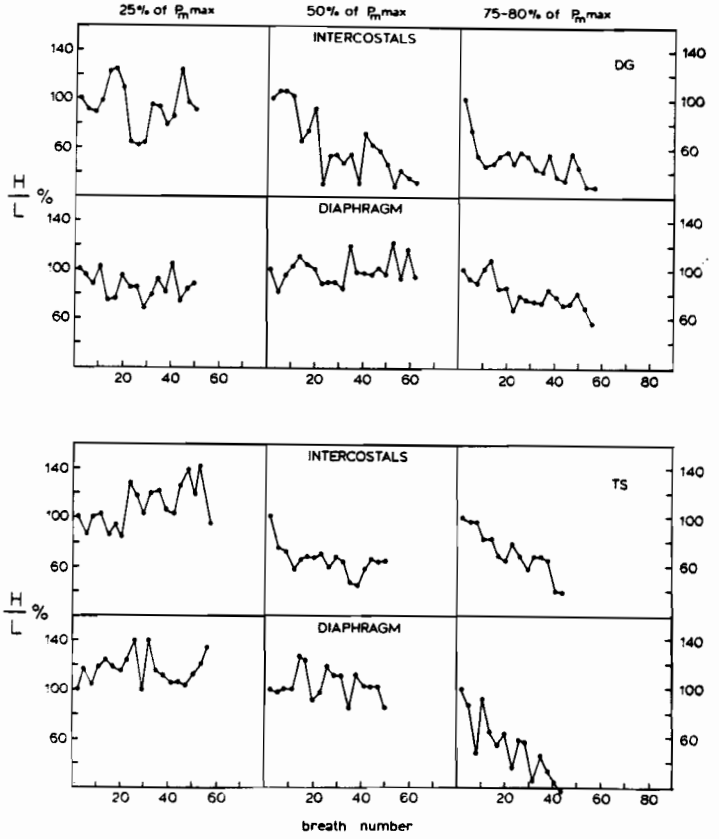

Figure 1: A) H/L ratio as percent of initial values is plotted for the intercostal muscles (open circles) and the diaphragm (closed circles) vs. breath number, when sustaining loads of 25% in left, 50% in middle, and 75% in right panels for Subject DG (top) and TS (bottom).

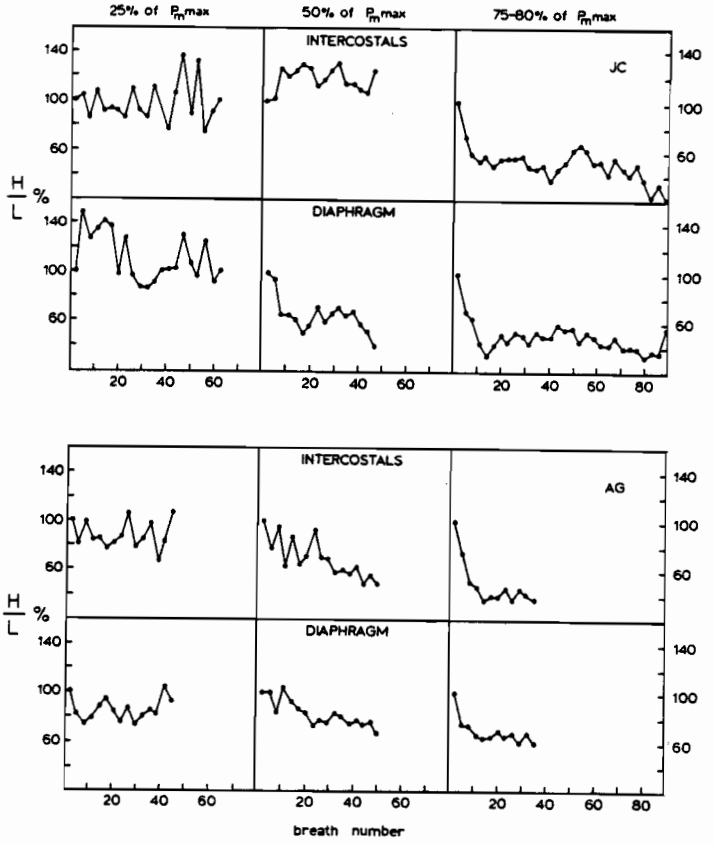

Figure 1: B) H/L ratio as percent of initial value is plotted for the intercostal muscles (open circles) and the diaphragm (closed circles) vs. breath number, when sustaining loads of 25% in left, 50% in middle and 75% in the right panels for subjects JC (top) and AG (bottom).

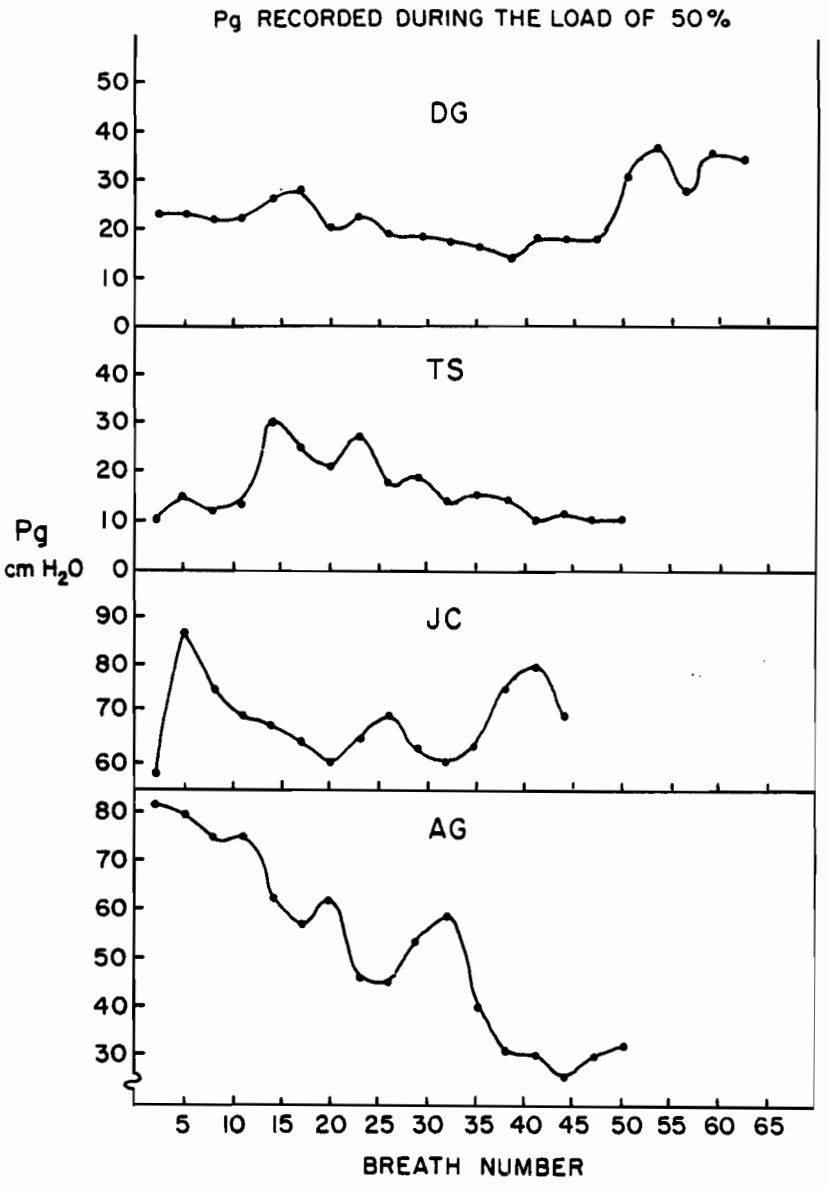

Figure 2: Gastric pressure (Pg) in cmH_20 is plotted as a function of breath number for the 4 subjects (a subject in each panel), when sustaining a load of 50% Pm_{max}, for which the EMG changes are shown in Figure 1.

ratio with time was steeper at this load than at 50%.

Figure 3 shows an example of the effect of sustaining a resistive breathing load at 50% of Pm_{max} predominantly using the intercostals (left panel), predominantly using the diaphragm (middle panels) and spontaneously using both groups of muscles (right panel). The tracings of H/L as a function of time are shown for the intercostal muscles (top tracing) and for the diaphragm (bottom tracings). When the subject selectively recruited the rib cage musculature in order to sustain the load (as indicated by a low Pg), a progressive decrease in the H/L ratio was observed for the intercostals and not for the diaphragm. However, when the diaphragm was selectively recruited for resistive ventilation at the same load, the EMG pattern of fatigue was observed in the diaphragm and not in the intercostals. When the subject was free to use both muscle groups and a spontaneous interaction could occur, a small and very gradual decrease in the H/L ratio with time was observed in the tracings made for the intercostal muscles. The Pg was generally low except for periodic increases. Thus, changes in the H/L were observed in the intercostals training and not the diaphragmatic one.

The more gradual decrease in the H/L ratio observed during spontaneous breathing could be attributed to the phenomena of recruitment and derecruitment of these two muscles (238,239).

To assess the EMG pattern of fatigue and subsequent recovery between interacting inspiratory muscles,

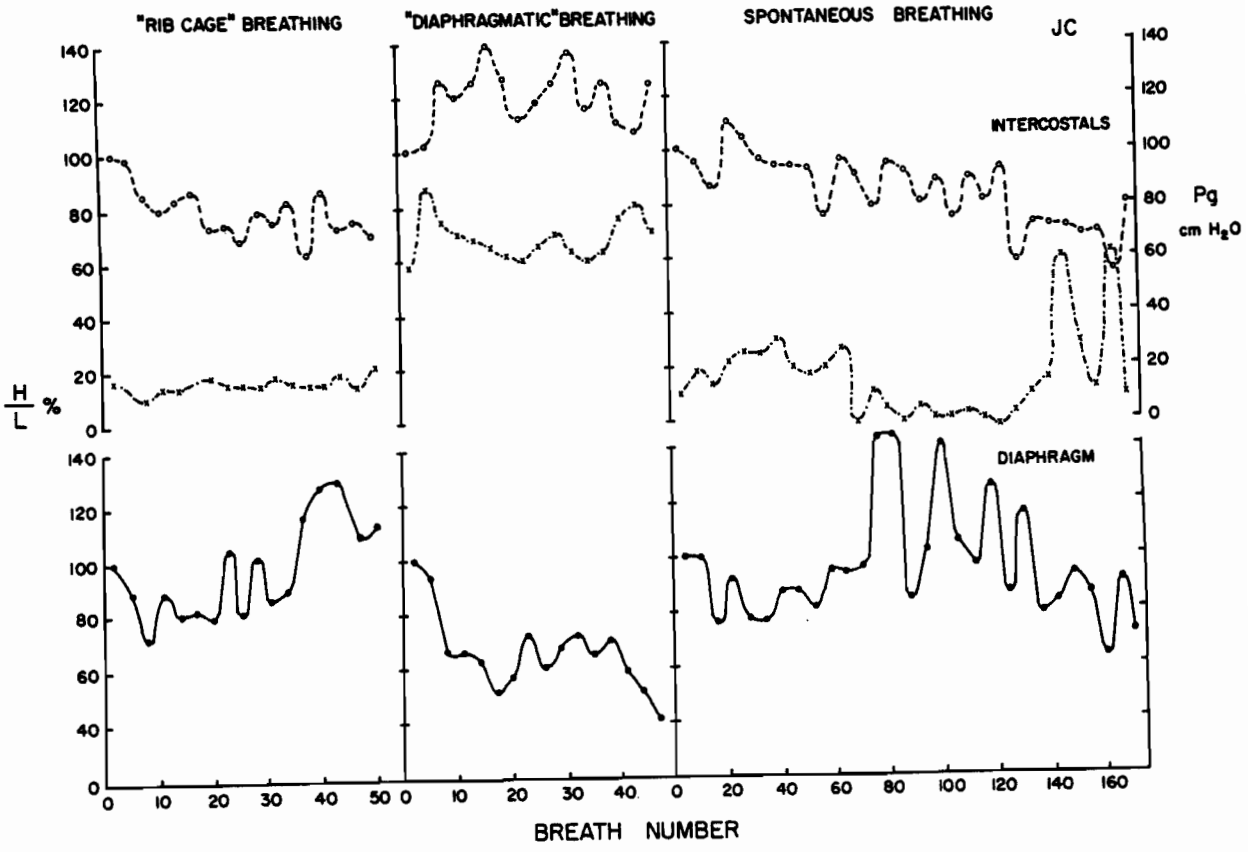

Figure 3: H/L ratio expressed as percent of initial value is shown for the intercostal muscles (o——o) and the diaphragm (●——●) as well as the Pg (x——x), plotted against breath number in one subject. The three panels show predominantly rib cage breathing (left panel), diaphragmatic breathing (middle panel) and spontaneous breathing (right panel).

we asked one subject to breath for 30 inspirations predominantly with the diaphragm and subsequently switch to predominantly the intercostals for 30 more inspiration. The results are shown in Figure 4. When the subject inspired predominantly with the diaphragm a progressive decrease in H/L was observed for the diaphragmatic electromyograms. No change was evident for the intercostals. When the subject switched to "rib cage" breathing a very rapid and drastic increase in the H/L ratio was observed in the diaphragm and within 6-9 inspiration complete recovery was apparent. At this point an EMG fatigue pattern was evident in the intercostal muscles.

e. Discussion

Respiratory muscle efficiency has been found to diminish in patients with severe airways obstruction (56,195). This requires a greater energy consumption by the respiratory muscles due to both increased work and decreased efficiency. Under these circumstances skeletal and inspiratory muscle fatigue is a reasonable possibility. Sharp et al (256) proposed, based on their observations on patients with chronic obstructive lung disease, that exhaustion of inspiratory muscles might be a factor in hypercapnia and that failure of the inspiratory pump might be an important contributing factor in respiratory failure. Therefore, a means of detecting inspiratory muscle fatigue had great potential clinical significance. Before accepting the H/L ratio of the inspiratory

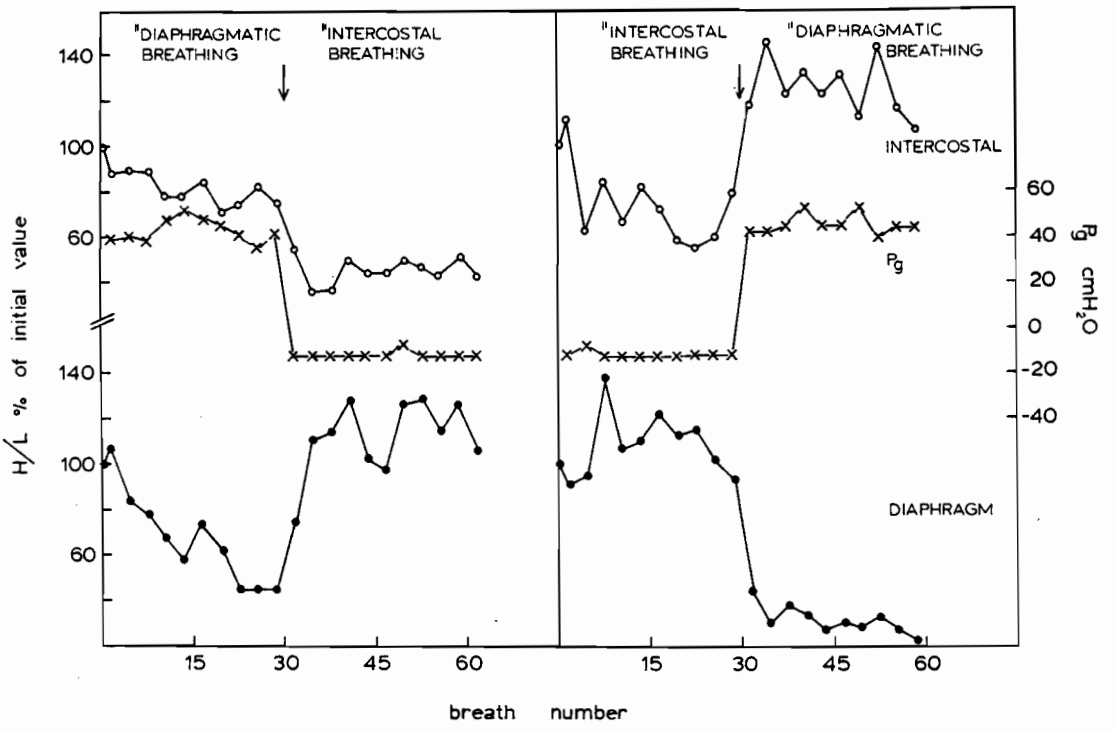

Figure 4: The H/L ratio expressed as percent of initial value is shown for the intercostals (top tracing; o——o), and diaphragm (bottom tracing, ●——●), as well as Pg (in the middle, x——x) is plotted against breath number for one subject (LE). The two panels (left and right) describe the maneuvers, ie., breathing first with "diaphragm" and switching to "intercostal" breathing (left panel) and vise versa (right panel).

muscles as a potential diagnostic tool, some potential sources of error had to be considered.

Since the fibers of the pectoralis major run above those of the intercostal muscles in the parasternal region we wished to eliminate the possibility that the intercostal electrodes would pick up myoelectric activity from the pectoralis major and hence mask the intercostal EMG pattern of fatigue. Theoretically it is unlikely that this muscle would give a fatigue signal because the force being generated by this muscle during resistive breathing is almost certainly well below the critical load at which dynamic fatigue would be developed. Nevertheless, in order to exclude this possibility we recorded the EMG activity of the internal intercostal muscles using fine wire intramuscular bipolar electrodes, employing standard techniques (24) in two subjects. These electrodes were placed at the same location as the upper intercostal surface electrodes. In addition, we recorded the EMG activity of the pectoralis major with a bipolar fine wire electrode inserted in the bulk of the muscle approximately at the midclavicular line at the level of the second intercostal space. The results of this experiment (see Figure 5), demonstrated that there was minimal or no EMG activity recorded from the pectoralis major muscle during resistive breathing; while the intercostal muscles were evidently active, as portrayed by the clear EMG signal recorded with both surface and fine wire intercostal electrodes. Therefore, we concluded that activity of the pectoralis major muscle during resistive breathing did not

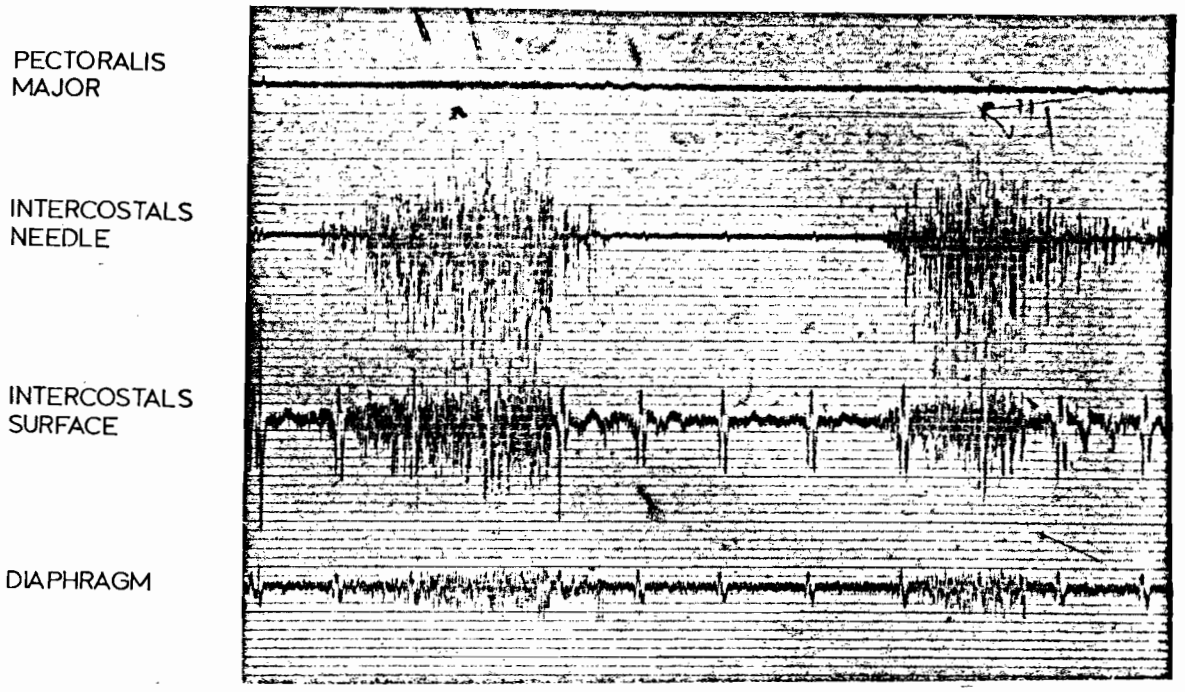

Figure 5: The EMG activity of all recorded muscles is shown: the pectoralis major (top tracing) intercostals recorded with fine wire needle electrodes (second tracing from top), intercostals surface recording (third tracing) and that for the diaphragm (bottom tracing).

interfere with the detection of fatigue by surface electrodes placed over the inspiratory intercostals. Similarly the myoelectric activity of the abdominal muscles might contaminate the diaphragm. However, we have previously shown (Chapter III.1 Results) that there was no change in H/L ratio of the abdominal EMG while the H/L ratio of both esophageal and surface electrode recordings of the diaphragmatic EMG fell. Other sources of possible error influencing the modifications in H/L ratios are:

1) Error due to changes in the electrocardiogram (ECG)
2) Error due to increases in the distance between the surface electrodes and the diaphragm.

In order to minimize the effect of the ECG on the low frequency component of the EMG, the ECG signal was gated manually. Thus, measurements were done during the period of diastole when the ECG contributed very little to the measured signal. This technique was described in Chapter III.1 (Methods).

In high lung volume the distance between diaphragmatic electrodes and the diaphragm may increase. A change in the distance between the measuring electrodes and the muscle was shown to influence the power spectra (182,183). It is not known if the phenomena occurs in the diaphragm, and if so to what extent it would affect the modification in the power spectrum as a result of fatiguing contraction. Consequently, we asked two subjects to perform a continuous isometric con-

traction, using the diaphragm, until the contraction could no longer be sustained. This maneuver was performed with the abdomen pushed out bringing lung tissue between the electrodes and the diaphragm, hence increasing the distance between the two. The other maneuver was to contract the diaphragm, pushing the abdomen in, preventing lung tissue from entering between the electrodes and the diaphragm. Figure 6 shows a typical example of the results from these experiments. The H/L ratio as percent of initial value is plotted against time for the EMG obtained with esophageal electrode (EE) and for that using surface electrodes (SE). The distance between the recording electrodes and the diaphragm can only increase for the surface electrodes. The results show that the changes in the H/L ratio for the two types of electrodes (EE, SE) vs. time are almost superimposed. Thus, we could assume that the increase in the distance between the diaphragm and the recording surface electrodes had minimal or no influence on the EMG pattern of fatigue. The decrease in H/L ratio represents a shift in the power spectrum towards the low frequency activity. This EMG pattern has been widely used in detecting fatigue in other skeletal muscles (125,138,149, 177). This pattern was reported to occur long before exhaustion and is not observed when non-fatiguing loads are sustained.

Roussos et al (239) estimated that the critical mouth pressure was between 50 and 70% of Pm_{max} when normal subjects were asked to breath against fatiguing loads at the mouth in a manner identical to the present experiments. When the

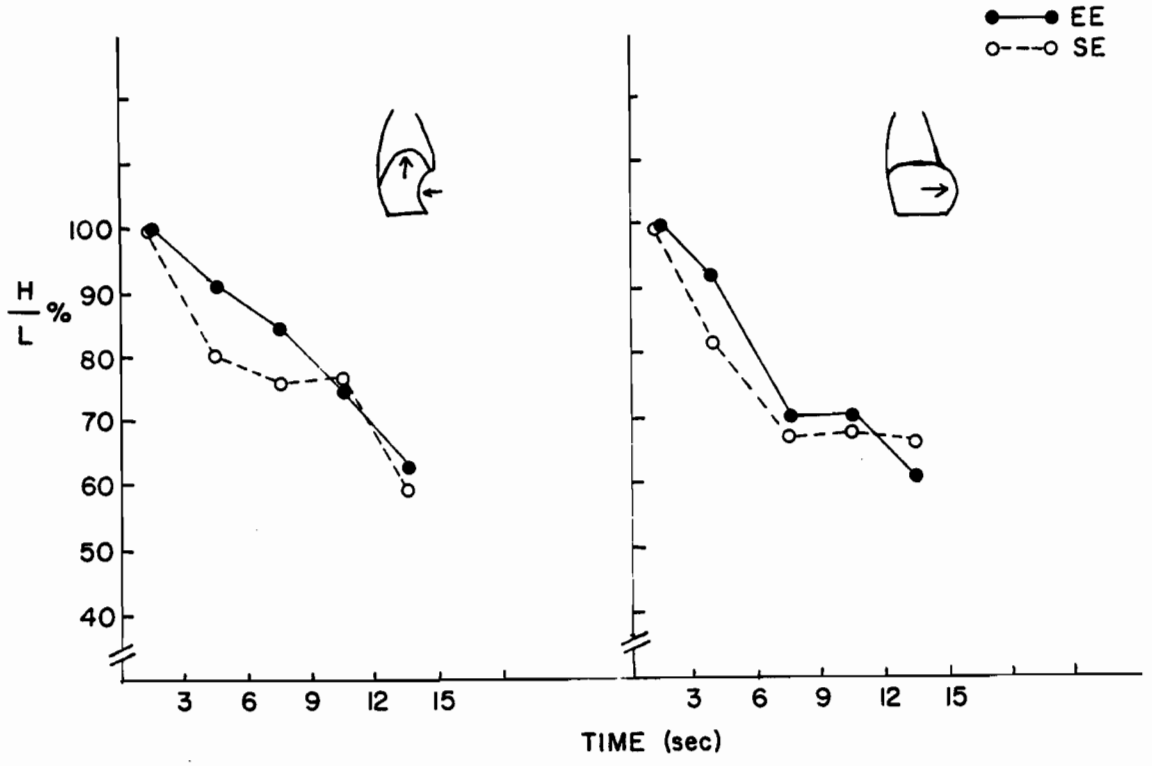

Figure 6: H/L as % of initial value ratio is plotted against time in seconds for the esophageal electrode (closed circles) and skin electrodes (open circles), during diaphragmatic isometric contraction with the abdomen pulled in (left panel), and the abdomen pushed out (right panel).

subjects were instructed to keep a constant Pdi with each breath the critical Pdi was 40% of maximum (238). This difference is probably explained by the fact that in the former study the subjects were free to use any inspiratory muscles they wished, whereas in the latter they were constrained to carry the load with the diaphragm. Roussos et al also presented data that there was cyclic recruitment and derecruitment of intercostal/accessory muscles, so that with recruitment there was relative relaxation of the diaphragm, whose force of contraction increased when the intercostal/accessory muscles were derecruited. If derecruitment results in electrophysiological recovery from fatigue, then reciprocal variations in H/L ratio of diaphragm and intercostal/accessory muscles would be expected.

Our results demonstrate that when high loads are sustained both groups of muscles, diaphragm and intercostals are highly active and the EMG pattern of fatigue was observed in both muscles. This is in agreement with previous observations that this load leads to exhaustion of the inspiratory muscles. However, when moderate loads were sustained, only the predominantly contracting muscle showed the signals of fatigue. With spontaneous breathing at this load recruitment and derecruitment of diaphragm and intercostal/accessory muscles occurred and only small changes in the H/L ratio resulted, and these were often reciprocal. This was in contrast to the observed significant decrease in H/L ratio when one muscle was predominantly used.

Additional evidence regarding the effect of recruitment and derecruitment on the delay in the onset of fatigue is the rapid recovery that was observed in the EMG pattern of fatigue when the subject switched from predominantly using one muscle to the other. This rapid recovery supports the hypothesis proposed by Roussos et al (239) that when the Pab decreased, indicating greater use of intercostal muscles, the diaphragm will recover rapidly. Rapid recovery after stopping exercise was observed in other skeletal muscles using spectral analysis (125). Since the muscles can recover very rapidly and in light of the data shown that during spontaneous resistive breathing the degree of change in H/L ratio is greatly reduced,it can be concluded that recruitment and derecruitment of inspiratory muscles during resistive breathing is likely to delay fatigue.

The minimal value for estimated critical pressure was found by Roussos et al (239) to be 50%. The critical pressure was defined as the pressure that could be sustained indefinitely without fatigue resulting. However, we observed the EMG pattern of fatigue at this load. It was demonstrated, using other skeletal muscles,that whenever a fatiguing load is sustained that shift in the power spectrum would be observed. That being the case,it could be suggested that if these loads were sustained for longer periods than in the study by Roussos et al (239), fatigue might have eventually resulted. Alternatively it may be that small shifts in the

EMG frequency spectrum occur when a muscle is performing close to but not quite at a level which leads to fatigue.

As a result of our studies we conclude that when the respiratory system sustains low loads the EMG frequency spectrum of the inspiratory muscles does not shift. However, when the respiratory system is loaded with a high fatiguing load both groups of muscles, the intercostals/accessory muscles and the diaphragm, show a reduction of the H/L ratio indicating a shift in the frequency spectrum to lower frequencies. When switching from breathing with one group of muscles to the other, electrophysiological recovery from fatigue is observed which may postpone the onset of fatigue. Thus spectral analysis of inspiratory muscle EMG has considerable potential as a diagnostic tool in detecting inspiratory muscle fatigue in clinical situations.

III.3 The Effect of Training on Strength and Endurance of the Diaphragm in Quadriplegia

a. Summary

Previous studies of inspiratory muscle EMG have shown that the ratio of the amplitude of the high frequency (150-350 Hz) to the amplitude of the low frequency (20.0-46.7 Hz) components (H/L) can be used to detect inspiratory muscle fatigue.

We used H/L ratio to detect fatigue of the diaphragm and sternocleidomastoid in 6 chronic quadriplegics (lesion C_3-T_1), while they breathed for 10 minutes against inspiratory resistances of 8, 10, 20, 36, and 96 $cmH_2O/l/s$. We measured the maximum inspiratory mouth pressure at FRC (Pm max) and from the EMG we estimated the critical inspiratory mouth pressure (Pm_{crit}) below which the EMG changes of diaphragmatic fatigue do not develop. The measurements were repeated after 8, 12 and 16 weeks of inspiratory muscle training consisting of inspiring for a period of 30 min daily, 6 days a week against a resistance just sufficient to produce the EMG changes of fatigue. Before training Pm_{max} was 62 $\pm$ 16 cmH_2O and Pm_{crit} was 11-21% of Pm_{max} (normal: 50-70%). During training Pm_{max} increased progressively and significantly ($P < .01$) for 12 weeks to a value of 83$\pm$ cm H_2O after which it reached a plateau. Pm_{crit} also increased progressively and significantly ($p < .01$) for 16 weeks both in absolute values and as a percent of Pm_{max} so that after

training Pm_{crit} was 21.5-32.8% Pm max fatigue signals. We concluded that: 1) Quadriplegics are predisposed to the development of inspiratory muscle fatigue due not only to reduced muscle strength but also to a reduction in endurance below that expected for their strength. 2) In these patients inspiratory muscle training increases both their strength and endurance and protects against fatigue.

b. Introduction:

It has recently been demonstrated that it is possible to produce fatigue of the inspiratory muscles of normal subjects by breathing against added inspiratory resistive loads (239). When this occurs the diaphragmatic electromyogram (EMG) changes so that the amplitude of the low frequency component (L) increases, while that of the high frequency components (H) decreases. The ratio of these amplitudes (H/L) which is independent of strength of contraction, is therefore a useful predictor of fatigue particularly as it falls substantially before the muscle has reached its limit of endurance (121). On the other hand, Leith and Bradley (177) showed that both endurance and strength of the inspiratory muscles increased following appropriate training. These observations have potentially important pathophysiologic and therapeutic implications. On the one hand, patients with an increase in the work of breathing and/or a decrease in inspiratory muscle strength may be predisposed to the development of fatigue which, if it

occurs, may lead to acute respiratory failure. On the other hand, training the inspiratory muscles in such patients may protect them against fatigue.

Quadriplegics represent just such a group of patients who are potentially at risk to develop inspiratory muscle fatigue. The work of breathing is increased due to a reduction in compliance (29,101) and most of the rib cage musculature is paralyzed, so that inspiratory muscle weakness is prominent. Hypoventilation is not uncommon in quadriplegia (29) and acute respiratory infections which may increase the work of breathing still further, are a frequent cause of death (263).

We have therefore studied quadriplegic patients in an attempt to measure the level of added resistive load which produces inspiratory muscle fatigue and the effects of inspiratory muscle training on strength and endurance.

c. Methods and Procedures:

Subjects: We studied four male and two female quadriplegic patients who ranged in age from 18 to 41 years, all of whom had a traumatic lesion to the cervical spinal cord at levels between C_{III} and T_I (Table 1). All patients were at least one year post injury, so that they all showed physiological and psychological stabilization (263). None of the patients had a previous history of lung disease. Lung roentgenograms were normal and chest physical examination revealed no signs of respiratory disease at

TABLE I

Respiratory Muscle Function Prior to Training

Subject	Vital Capacity l	Pm_{max} cm H_2O	R^1	Pm_{crit} cm H_2O	Pm_{crit} % of Pm_{max}	Level of lesion
MB	1.1	50	10	5.0 - 6.8	10 - 14	C_3 - C_4
MT	1.35	52	10	5.5 - 6.8	11 - 13	C_3 - C_4
KD	1.8	60	36	9.7 - 11.8	16 - 20	C_5 - C_6
GM	3.4	80	10	8.1 - 11.3	7 - 14	C_6 - C_7
BC	2.4	84	96	11.2 - 17.4	13 - 21	C_7 - T_1
FP	2.7	60	10	5.5 - 6.4	9 - 11	C_4 - C_5
Mean	2.1	64		7.1 - 10.1	11 - 15.5	-
Normal Values		110-150		70 - 87	50 - 70	-

R^1 - the lowest value of resistance which produced diaphragmatic fatigue

Pm_{max} - maximum negative inspiratory mouth pressure at FRC

Pm_{crit} - Inspiratory mouth pressures just sufficient to produce fatigue. The true value falls between the two pressures given in the column. (See text for further detail).

the time that they were studied. The ECG was normal and apart from the quadriplegia there was no clinical evidence of other systemic disease.

Preliminary Investigations: In a preliminary study we used EMG's to determine which of the following muscles were most active during inspiratory resistive breathing: diaphragm, inspiratory intercostals, sternocleidomastoid (SCM), pectoralis major and trapezius. The EMG was recorded on the right side using bipolar surface electrodes (Beckman 255-083547-A). The electrodes to record the EMG of the diaphragm were placed on the 6th and the 7th intercostal spaces as described in Chapter II.1 (Methods). The electrodes for the intercostal muscles were placed in the 2nd and 3rd right intercostal spaces parasternally. For the other muscles the electrodes were placed 2.5 cm apart over the middle portion of the muscles along the direction of the fibers. It was observed that the muscle constantly involved in resistive breathing was the diaphragm and occasionally the SCM, and thus during the fatigue and endurance studies we only analyzed the myoelectrical activity of these muscles.

Initial Measurements: Inspiratory muscle strength, endurance and vital capacity (VC) were measured in all patients while they remained seated in their wheelchairs.

For the purpose of evaluating the inspiratory muscle strength the patients were asked to make a maximum inspiratory effort at FRC against an occluded airway. The resultant peak mouth pressure (Pm) was measured with a water

manometer and the highest value of three trials was assumed to be the maximum that could be developed at FRC (Pm_{max}). Vital capacity (VC) was measured using a 10 litre Collins spirometer and was taken as the highest of three trails.

In order to determine the endurance of the inspiratory muscles and the lowest values of resistance which produced the electromyographic changes of diaphragmatic fatigue (R), the patients breathed through a series of inspiratory resistances placed on the inspiratory line of a Hans-Rudolph valve. The resistances used were non-linear with values of 8, 10, 20, 36, 60 and 96 cm $H_2O/l/s$ measured at a flow of 0.25 l/s. Expiration was unloaded and each patient was free to choose his own rate and depth of breathing.

The patient breathed through the resistance for 10 minutes. During each run we measured Pm relative to atmospheric pressure using a differential pressure transducer (Sanborn 267B) and flow at the mouth by a pneumotachograph (Fleisch no. 3) coupled to a differential transducer (Hewlett Packard 270) in addition to diaphragmatic and sternocleidomastoid EMG. These were recorded throughout each fatigue test on a four channel tape recorder for further analysis (HP instrumentation recorder 3960) as well as on an ultraviolet light sensitive visicorder (Honeywell 1508) in order to be able to detect contaminating noise. End tital PCO_2 was monitored using a CO_2 meter (Beckman Medical Gas Analyzer LB). The experimental set up is shown in Figure 1.

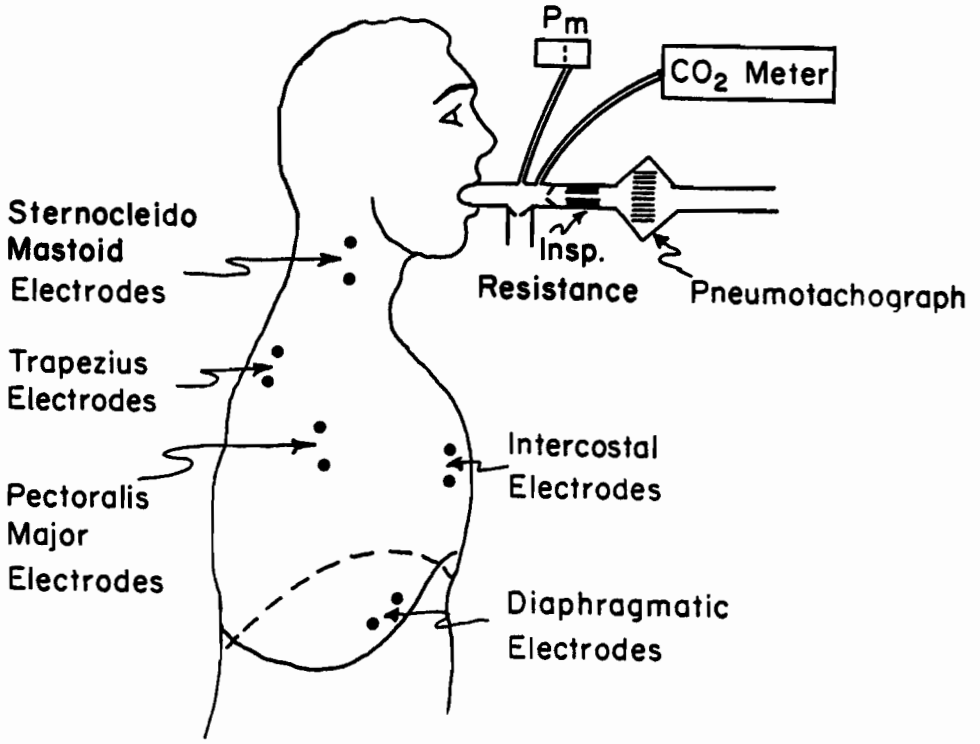

Figure 1: Experimental design showing location of the EMG electrodes, the mouth pressure (Pm) air flow at the mouth and the location of the resistance.

Each patient rested for one half hour between each run in order to allow for recovery. No more than three resistances were tested in one day, after which the electromyograms were analyzed for fatigue signals before proceeding to the next level of resistance. The lowest resistance, producing electromyographic evidence of diaphragmatic fatigue (R') was used in the training program.

EMG Recording and Analysis: The diaphragmatic and sternocleidomastoid EMG were recorded and conditioned by differential amplifiers with band pass filters of 8 to 1000 Hz and an amplification factor of 1000. The signal from the preamplifier was recorded simultaneously on the tape recorder and the visicorder. The signal from the tape was subsequently passed through two band-pass filters with ranges from 20.0 to 46.7 Hz for the lower frequency component and 150 to 350 Hz for the high frequency component. Another wide band pass output filter (10-1000 Hz) was used to measure the total EMG (T). the filtered signal was rectified, integrated (time constant = 0.1 sec) and recorded on a strip recorder for further analysis (see Fig. 2).

During each inspiration an average amplitude of the H, L, and T was estimated by taking the mean value of amplitudes measured at the beginning, middle and end of each breath in which mouth flow was relatively constant. The ECG signal was manually gated by not measuring the EMG during the QRS complex and the average H/L ratio of three consecutive breaths were computed. The procedure is the same as previously described (Chapter III.1, Methods).

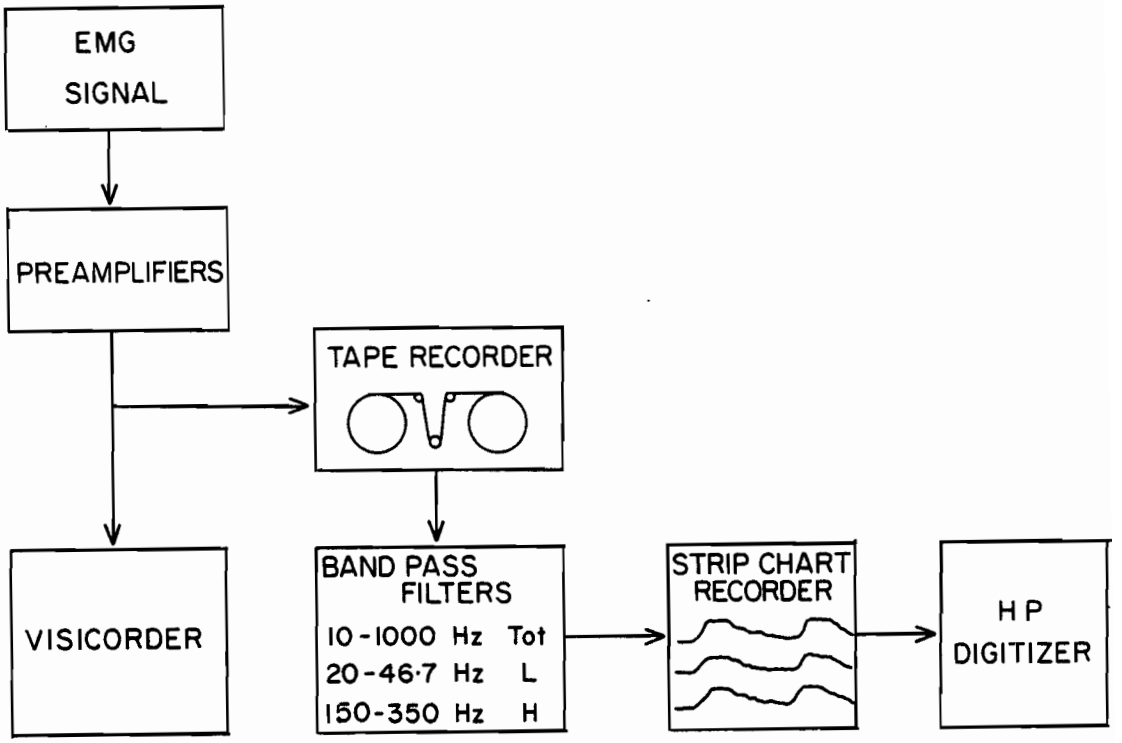

Figure 2: Diagrammatic representation of the EMG singal processing.

Training Program: Once the level of fatiguing resistive load (R1) was known for each individual, the subjects began the inspiratory muscle training program. This consisted of breathing for two 15 minute sessions daily, with a noseclip in place, through a Hans-Rudolph valve with R' placed on the inspiratory line. This program was conducted 6 days a week, for 8 weeks. Patients reported twice weekly to the laboratory for follow-up and EMG recordings were made by a physiotherapist who was part of the research team.

At the end of the 8 week training period the patients underwent the same test protocol as in the pre-training tests in order to evaluate whether the training had modified inspiratory muscle strength as assessed by Pm max, endurance as assessed by the EMG, and vital capacity. As we found that breathing through R' no longer resulted in fatigue we decided to continue the training for 8 more weeks with a greater resistance (R'') in order to determine whether training at a higher load would produce a further improvement. For this purpose a new R' was determined for each patient (R''), and training with this resistance was continued as before. Two post-training evaluations, after four and eight weeks of training with the second resistive load were conducted, using the same experimental protocol as previously. As the sternocleidomastoid muscle was used less after training than before, minimal or no EMG activity recorded from the SCM was observed, therefore we concentrated our analysis on diaphragmatic EMG during our subsequent experiments.

d. Results

An example of the changes in the H/L ratio with time, breathing without resistance (top panel) and against two levels of resistance (middle and bottom panels) are shown for two patients in Figure 3.

When the patients inspired without a resistance, there was no reduction in the H/L ratio with time suggesting that inspiratory muscle fatigue did not develop. However, breathing through a resistance of 10 and 36 cm H_2O/l/sec resulted in a progressive decrease in the H/L frequency ratio with time, indicating the development of diaphragmatic fatigue.

Table 1 gives the results of the initial studies in each individual. We defined Pm_{crit} as the minimal level of mouth pressure during inspiration, which produced a decrease in the H/L ratio, indicating fatigue. Its value fell between the mouth pressure that was developed while breathing through R' and that during breathing through the next lower level of resistance. Thus Pm_{crit}, expressed in both absolute values and as a percentage of Pm_{max}, falls between the two values given in the appropriate columns of Table 1.

Several differences between normal subjects and quadriplegics appear in this table. First, there is a reduction in inspiratory muscle strength, as reflected in the less negative values of Pm_{max} in the quadriplegics. This is responsible for part of the reduction in VC. Secondly, there is a reduction in Pm_{crit} and finally, the reduction in Pm_{crit} is more than can be accounted for on the basis of muscle weakness alone. That is, Pm_{crit} expressed as a percentage of Pm_{max} is also markedly reduced.

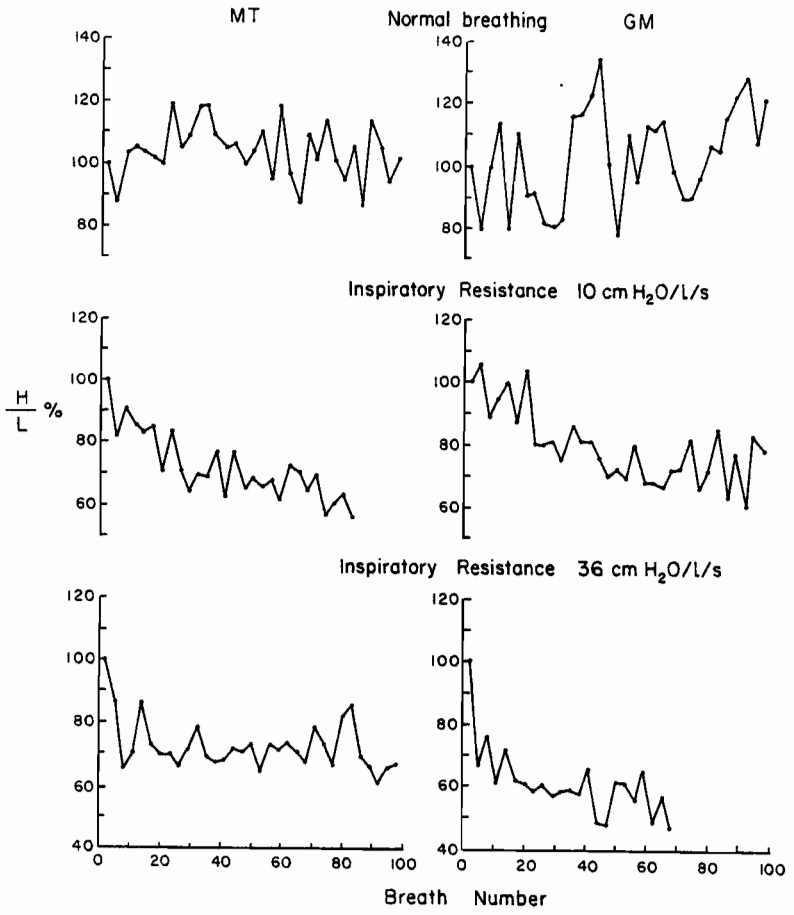

Figure 3: An example of the changes in H/L ratio as a function of breath numbers in quiet normal breathing top panel and in resistive breathing middle and bottom panels in two patients: MT (left side) and GM (right side). The points plotted are average of every 3 breaths.

Following the first 8 weeks of training period, there was no fall in the H/L ratio with time while breathing through R'. A comparison of this ratio before and after training is shown for all subjects in Figure 4. In all patients, the pre-training progressive decrease in the H/L ratio of the diaphragmatic EMG with time was absent in the post-training run. This could be interpreted as indicating that the patients did not develop diaphragmatic fatigue when they sustained the same load that caused fatigue before training. Thus, the diaphragm increased its endurance. Figure 5 shows the EMG pattern with the second resistive load, namely after 8 and 16 weeks of training. It indicates that endurance further improved as a consequence of continuing training with higher loads.

Figure 6 shows the changes in Pm_{crit} and Pm_{max} as a function of time during the training period. The changes in these values were statistically significant ($p < .01$). The increase in Pm_{crit} indicates improved endurance, while the increase in Pm_{max} indicates increased strength. It should be noted that the increase in endurance is not solely related to the increase in strength as Pm_{crit} as percent of Pm_{max} increased from between 11.2 - 15.5% Pm_{max} to between 21.5 - 32.75% Pm_{max}.

Some of the patients complained of shortness of breath while eating, and fatigue after three hours of sitting in their wheelchairs before the training period. Both of these complaints disappeared as training progressed. Thus, in

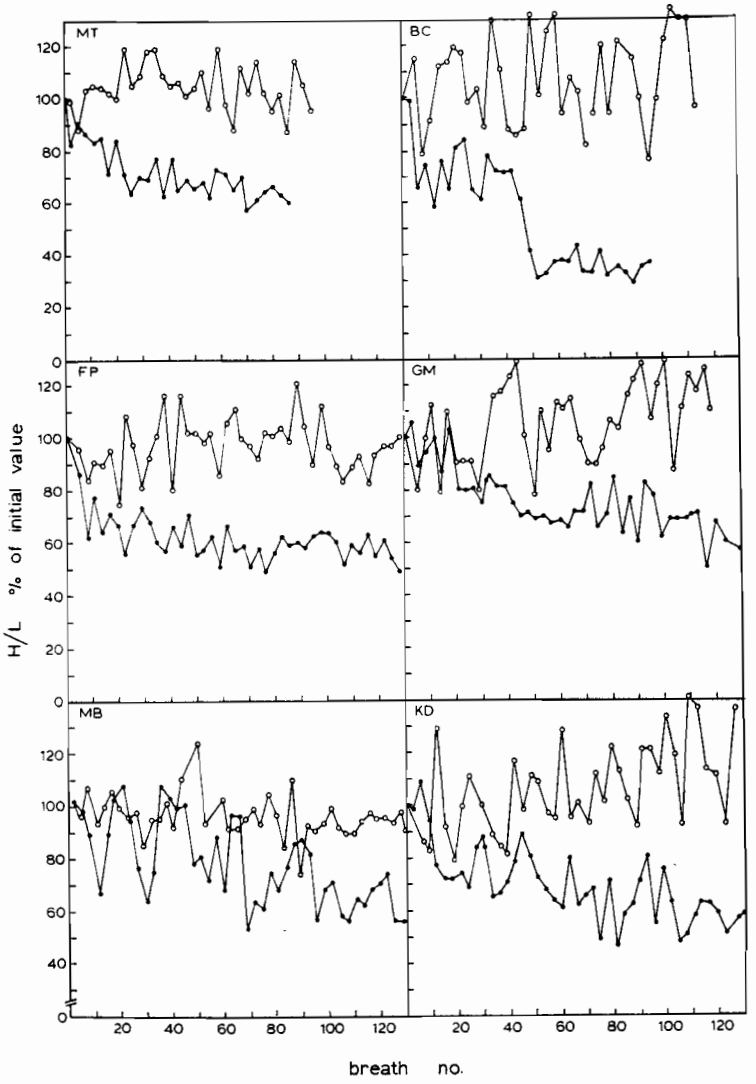

Figure 4: The H/L as percent of initial value as a function of breath no. for 6 individual patients (a patient in each panel) for the pretraining data (closed circles) and post training data at 8 weeks (open circles).

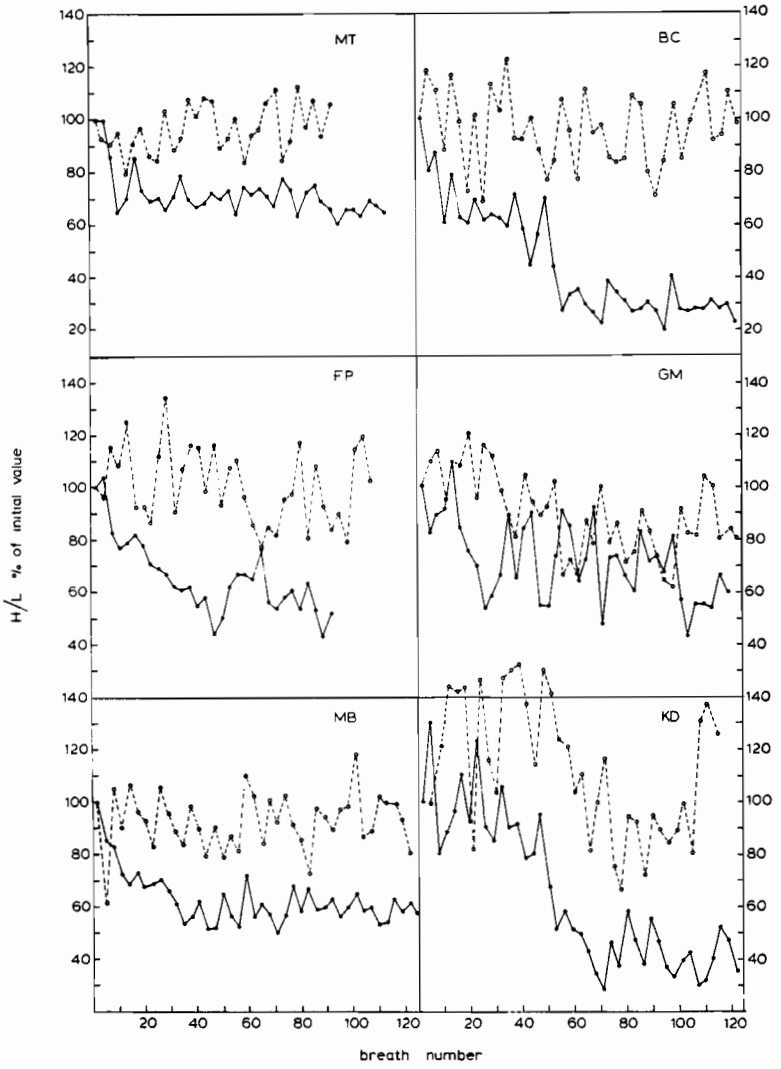

Figure 5: The H/L as percent of initial value as a function of breath no. for 6 individual patients (a patient in each panel), for the data obtained at 8 weeks, prior to training with higher resistive load (closed circles) and the data obtained at 16 weeks (opened circles).

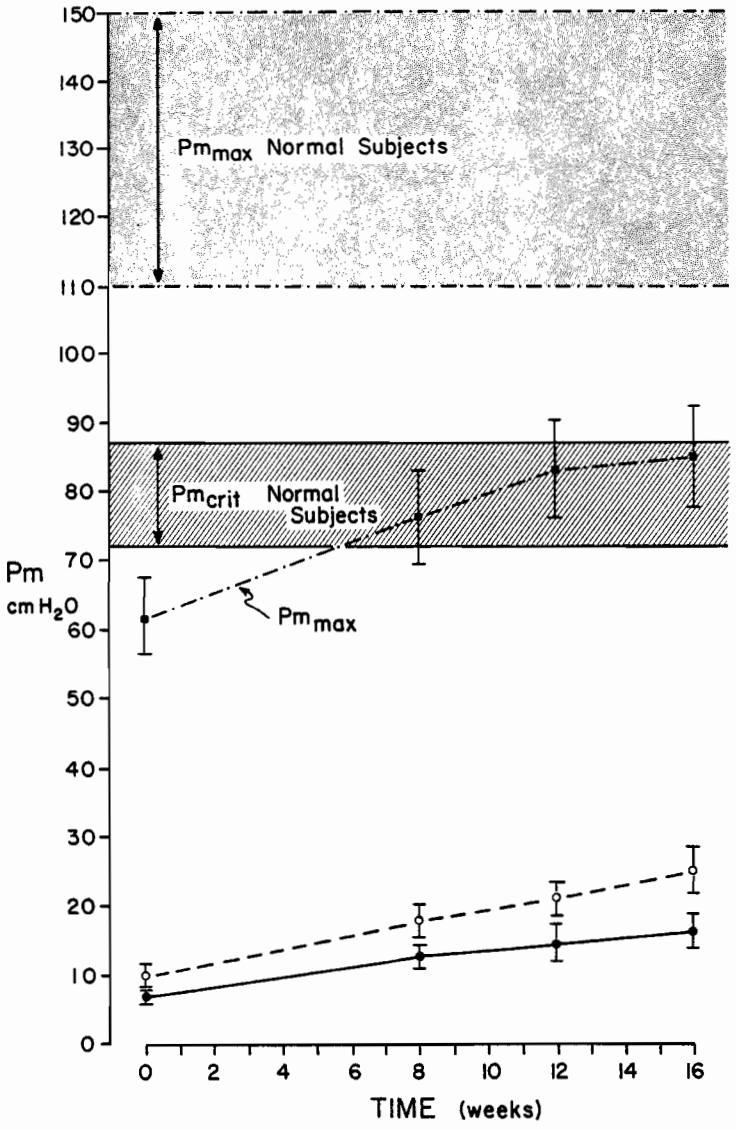

Figure 6: Pm in cmH_2O as a function of time in weeks. Top shaded area is the range of Pm_{max} for normal subjects. The change in Pm_{max} for quadriplegic patients is shown by square symbols and solid lines; lower shaded area is Pm_{crit} for normal subjects. The mean values and SE for the Pm developed with each inspiration during resistive breathing which did not produce fatigue in quadriplegic patients (closed circles and solid lines), mean values of SF and Pm developed with each inspiration during resistive breathing which produced fatigue in quadriplegic patients (opened circles and broken lines).

addition to the observed changes in endurance and inspiratory muscle strength, there was symptomatic improvement as well.

e. Discussion

Paralysis of some of the inspiratory muscles leads to a decrease in inspiratory force limiting the inspiratory capacity and accounting for part of the reduction in vital capacity (VC) characteristic of quadriplegia (29,100,102, 101). We found the maximum static inspiratory pressure (Pm_{max}) to be reduced to about 2/3 of the normal value, results similar to those previously reported (100,102).

In addition to a reduction in strength, the mechanical properties of the chest wall are altered as a result of the paralysis (101). Stiffening of the rib cage takes place early after injury. Furthermore, there is a reduction in lung compliance (29). Both of these lead to an increase in the work of breathing (29).

The combination of inspiratory muscle weakness and breathing against an increased load are presumably major factors predisposing to the development of inspiratory muscle fatigue (155). One of our objectives in the present study was to test this hypothesis. As an index of fatigue we used the decrease in the H/L ratio (a consequence of the shift in the power spectrum of the EMG). This is a well-defined phenomenon in skeletal muscle fatigue (153) which we recently adapted to detect fatigue of the diaphragm (121).

With the development of fatigue the amplitude of the high frequency components of the EMG diminishes while that of the low frequency components increase. Thus, there is a progressive fall in the ratio of the amplitudes of the high to low frequencies. This ratio remains constant when skeletal muscles and diaphragm are working at nonfatiguing levels, and which is essentially independent of force of contraction when the muscle is not fatigued (121). When a muscle is working at a fatiguing level the EMG power spectrum shifts as reflected in a decrease in H/L. As it occurs before the muscle has reached the limit of its endurance, and because the method is non-invasive, electromyography would seem to have great promise as a means of detecting inspiratory muscle fatigue in patients with respiratory disease. There can be little doubt in our patients, that the progressive decrease in H/L was due to diaphragmatic fatigue, because in quadriplegia, the diaphragm is the only muscle which could produce such signals in the 6th and 7th intercostal spaces.

Using the H/L ratio as the criterion, we found that diaphragmatic fatigue developed in quadriplegics when inspiratory mouth pressure was 6.8 to 17.4 cmH_2O during resistive breathing, whereas in normal subjects a negative mouth pressure of 70-87 cmH_2O was required (239). Thus, in quadriplegia the inspiratory muscles fatigue at much lower loads than they do in normal subjects. This is due, in part, to the reduced muscle strength of quadriplegics whose maximum negative mouth pressures at FRC were only about 2/3 the

value of normal subjects. Clearly, however, the decrease in muscle strength per se, does not account entirely for the easy fatiguability of the diaphragm in quadriplegia, as the Pm_{crit} expressed as a percentage of Pm_{max} was also much less in quadriplegics than in normals.

There are a number of possible reasons for this finding. The first is technical. Pm_{crit} in normal subjects was not estimated electromyographically, but by exercising the respiratory muscles to exhaustion on a number of occasions and extrapolating the data to an infinite endurance time (238). Secondly, in normal subjects part of the load during resistive breathing can be carried by other respiratory muscles, while in quadriplegia the whole load must be carried by the diaphragm and the sternocleidomastoid muscles. This restriction may influence endurance more than strength. Indeed it appears as if normal subjects alternate between primarily using the diaphragm and primarily using the intercostal/accessory muscles of inspiration when breathing against a fatiguing resistive load (238,239). This alternation, which cannot be achieved by quadriplegics, may protect against the development of fatigue.

As quadriplegics are limited to breathe almost exclusively with the diaphragm, a more appropriate comparison of Pm_{crit} is with the normal value of transdiaphragmatic pressure above which fatigue results. This is about 40% of maximum transdiaphragmatic pressure (238). However, it is difficult to compare this figure with the results in quadri-

plegics because, although diaphragmatic contraction produces a fall in mouth pressure which we measured, it also produces a rise in abdominal pressure which we did not measure. Thus, we can not make a valid estimate of critical transdiaphragmatic pressures in quadriplegics on the basis of the present measurements. Nevertheless, because diaphragmatic work required for quiet breathing in quadriplegia is already substantially increased (29), it may be that the added resistive load sufficient to produce fatigue, is substantially reduced.

Finally, it is possible that because of the enforced inactivity, there is atrophy of the diaphragm. It is conceivable that muscle atrophy reduces the critical pressures expressed as a percent of maximum that a muscle can develop.

Our data show that an inspiratory muscle training program results in less symptoms and increased inspiratory muscle strength and endurance in quadriplegia. These changes will protect them against the development of fatigue as shown by significant increases in Pm_{crit} both in absolute values and as a percent of Pm_{max}. In addition, there were significant increases in Pm_{max}. Thus endurance was prolonged and this effect was greater than could be accounted for by the increase in strength alone.

The increase in Pm_{crit} as a percent of Pm_{max} with training in quadriplegia suggests the possibility that the individual fibers of the diaphragm have increased their oxidative capacity. There is certainly a correlation between diaphragmatic endurance and the fraction of slow

twitch high oxidative fibers in the diaphragm (179). Furthermore, Keens et al (160), showed that rats whose trachea were banded, thereby increasing the resistive work of breathing, responded with an increase in oxidative capacity, and a change in mitochondrial content and fatty acid oxidation by the diaphragm after 5 weeks. Similar results have been obtained for other skeletal muscles. Hollosey found a good correlation between performance and oxidative enzymatic activity. In addition, he showed that mitochondria are capable of adaptive changes in both composition and number (138). Lieberman et al (180) showed that treadmill running in guinea pigs increased the fraction of high oxidative muscle fibers in the diaphragm which suggests an increase in oxidative capacity. The results reported by Keen et al (132) and by Lieberman et al (180) suggest that the diaphragm responds to training by changing easily fatiguable fast twitch slow oxidative fibers to more fatigue resistant slow twitch fast oxidative fibers in order to achieve a more efficient contraction.

Other training programs have been described in quadriplegia; Fugl-Meyer (101) designed a method of treatment for the impaired ventilatory function in patients with high spinal cord transection emphasizing lung insufflation exercises. He observed improvement in inspiratory muscle strength and lung volumes. However, he did not measure the effect of the treatment on inspiratory muscle endurance.

There is not a direct one to one relationship between strength and endurance. Indeed, Leith and Bradley (172) showed that normal subjects can improve their inspiratory muscle endurance with a specific training program whereas a different type of training program increased strength. Keens et al (159) showed that either a program of specific ventilatory exercise or general upper body exercise improved inspiratory muscle strength and endurance in cystic fibrosis.

In both studies the method for training and assessing ventilatory muscle endurance was different from ours. They measured the length of time that subjects could maintain a predetermined fraction of the maximum voluntary ventilation under isocapnic conditions (276,291). This method is substantially more complicated, requires a good deal more patient co-operation, and cannot be carried out at home. Consequently, in consultation with Dr. David Leith we designed the resistive breathing training program, in which the patients require only a Hans-Rudolph valve with the appropriate resistance placed in the inspiratory line and a nose clip. Such equipment is light and portable and is readily acceptable by the patient and suitable for home use.

Since it is likely that training must be continuous in order to maintain an increased level of inspiratory muscle endurance (159) it is presumably important that quadriplegic patients, who generally have no other type of physical activity, continue in the training program indefinitely.

Inadequate inspiratory muscle strength and endurance are primary factors in the development of inspiratory muscle fatigue. We have shown that as a result of training, quadriplegic patients can sustain higher resistive loads without developing inspiratory muscle fatigue.

We suggest that specific inspiratory muscle training may protect the quadriplegic against the fatigue that may result from acute respiratory infection and which frequently results in death from respiratory failure.

CHAPTER IV

CONCLUSIONS

CONCLUSIONS

The conclusions drawn from the results found in the investigations reported in this thesis were as follows:

Normal Subjects

1) Diaphragmatic fatigue can be detected before exhaustion by measuring the changes in the ratio of the amplitude of high (H) to low (L) frequency components (H/L) of the EMG signal. With fatigue, there is a reduction of the H/L ratio which reflects a shift in the frequency spectrum.

2) The H/L ratio of the diaphragmatic EMG is independent of the Pdi when the diaphragm is not fatigued.

3) The H/L ratio decreases when the diaphragm performs fatiguing work, (50% and 75% Pdi_{max}), its reduction is more rapid at higher Pdi's (75% Pdi_{max}), and it does not change when sustaining nonfatiguing loads (25% Pdi_{max}).

4) Diaphragmatic fatigue can be detected by skin electrodes (placed on the 6th and 7th intercostal spaces) satisfactorily and reliably. Because this method is non-invasive and provides evidence of fatigue before the diaphragm fails as a pressure generator, it may prove useful in establishing a diagnosis of respiratory muscle fatigue in patients.

5) Both groups of muscles, diaphragm and intercostals are highly active when breathing against high resistive loads (75% Pm_{max}) at the mouth. Consequently, the EMG pattern of fatigue is observed in tracings obtained from both muscles. No change in the H/L ratio occurs for either muscle when non-fatiguing loads (25% Pm_{max}) are sustained.

6) When moderate loads are sustained (50% Pm_{max}) the EMG pattern of fatigue is observed from either the diaphragm or the intercostals, or both, depending which group of muscles are primarily active.

7) When switching from breathing with one group of muscles to another a complete recovery is observed on the EMG frequency spectrum of the non-active muscle (within 6-9 breaths). Thus, if recruitment and derecruitment of the inspiratory muscles during resistive breathing occurs, fatigue may be delayed.

Quadriplegic Subjects

8) Quadriplegic patients develop inspiratory muscle fatigue at much lower inspiratory resistive load than normals, both in absolute values and as percent of maximum , indicating inadequate inspiratory muscle endurance.

9) Training of the inspiratory muscles by resistive breathing produces an increase in inspiratory muscle strength and endurance, as demonstrated by increase in the Pm_{max}, Pm_{crit} and the absence of fatigue. Thus, inspiratory muscle training may protect these patients against the development of respiratory failure resulting from inspiratory muscle fatigue due to such causes as respiratory infections.

Statement of Originality

I believe that in this thesis the following original information has been provided:

1) Measurements of diaphragmatic and intercostal muscle fatigue by observing the changes in the ratio of the amplitudes of the high (H) to low (L) frequency components (H/L) of the myoelectric activity (EMG).

2) Detecting fatigue of the inspiratory muscles before the muscles fail as a pressure generator.

3) Detecting diaphragmatic and intercostal muscle fatigue by noninvasive skin electrodes.

4) The observation of EMG pattern of inspiratory muscle fatigue in quadriplegic patients at a significantly lower load than normals.

5) The measurement of critical mouth pressure (Pm_{crit}) in quadriplegic patients, indicating their endurance capacity.

6) The application of inspiratory resistive training program to improve quadriplegic patients inspiratory muscle endurance and strength.

7) The observation of increased inspiratory muscle strength and endurance with a resistive breathing training program in quadriplegic patients.

8) The observation that training increased the load at which the inspiratory muscles develop fatigue.

Assistance given by Co-authors

Chapter III.1.

1) EMG pattern of diaphragmatic fatigue

A. Grassino - assisted with the experiments and advice.

W.R.D. Ross - constructed the EMG equipment

P.T. Macklem - Research Director

Chapter III.2.

1) The EMG Pattern of Inspiratory Muscle Fatigue

A. Tsanaclis - Assistance with the experiments

A. Grassino

C. Roussos

P.T. Macklem - Research Director

Chapter III.3.

1) The effect of training on strength and endurance of the diaphragma in quadriplegia.

E. Riley - The physiotherapist who assisted in the training of the patients.

H. Ladd - consultant in relation to patients.

A. Grassino - Advice

P.T. Macklem - Research Director

APPENDIX

ABBREVIATIONS

α	- energy stored in the muscle
A-P	- anterior posterior diameter
ATP	- adenosine triphosphate
ATPase	- adenosine triphosphatase
β	- energy supplied to the muscle
C	- total energy consumed
$\dot{C}$	- rate of energy consumption
C_3-C_7	- cervical vertebrae number 3 to number 7
CO_2	- carbon dioxide
Di	- diaphragm
ECG	- electrocardiogram
Edi	- EMG of the diaphragm
EMG	- electromyogram
ERV	- expiratory reserve volume
FHO	- fast twitch high oxidative fibers
FLO	- fast twitch low oxidative fibers
FRC	- functional respiratory capacity
FTa	- fast twitch high oxidative fibers
FTb	- fast twitch low oxidative fibers
H	- amplitude of the high frequency component of the EMG signal
H/L	- the ratio of the high frequency to the low frequency components of the EMG
Hz	- cycles per second
IC	- intercostals
IEMG	- integrated electromyogram

L - amplitude of the low frequency component of the EMG

MVV - maximum voluntary ventilation

N - normal

N_2 - nitrogen

O_2 - Oxygen

P_{ab} - abdominal pressure

Pb - body surface pressure

Pdi - transdiaphragmatic pressure

PCO_2 - carbon dioxide tension

Pdi_{crit} - critical transdiaphragmatic pressure. The pressure below which no fatigue occurs.

Pdi_{max} - maximum transdiaphragmatic pressure

Pes - esophageal pressure

Pg - gastric pressure

PIC - pressure produced by the intercostal muscles

PL - transpulmonary pressure

Pm - mouth pressure

Pm_{crit} - critical mouth pressure

Pmus - pressure produced by the muscles

PO_2 - oxygen tension

Ppl - pleural pressure

Pr - pressure developed across the rib cage

QRS - QRS complex of the electrocardiogram

RC - rib cage

RV - residual volume

SCM - sternocleidomastoid

SD - standard deviation

SDH - succinic acid dehydrogenase

SE - standard error

SHO - slow twitch high oxidative fibers

ST - slow twitch fibers

T - total integrated EMG

TLC - total lung capacity

t lim - limit time, endurance

V - volume

$\dot{V}$ - flow

VC - vital capacity

VO_2 - oxygen consumption

V_T - tital volume

W - work

$\dot{W}$ - power

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