THE UNIVERSITY OF MANITOBA

RELATIONSHIP OF THE END TIDAL LEVEL TO THE DIMINISHED VENTILATORY RESPONSE TO CO_2 DURING RESISTIVE LOADING IN NORMAL SUBJECTS

by

HENRY WILLIAM EDSTROM, M.D.

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR

THE DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF PHYSIOLOGY

WINNIPEG, MANITOBA

July, 1972

TABLE OF CONTENTS

LIST OF FIGURES

PART II PAGE

PART I. A REVIEW OF THE LITERATURE

A. INTRODUCTION

Patients with chronic obstructive lung disease have a significant reduction in their ventilatory response to CO_2. Three hypotheses for this reduction have been postulated. I. It is the result of a reduction in the stimulation of the respiratory center because of an increase in the buffering capacity of the blood for hydrogen ion. II. Primary depression of the respiratory center exists. III. The reduction is due to alteration of the mechanics of the respiratory muscles and lungs.

Part II of this thesis reports studies carried out to determine if the diminished response to CO_2 during resistive loading could be attributed to the increase in lung volume which occurs in this situation.

B. THE NERVOUS CONTROL OF BREATHING

Breathing in man is a highly organized activity which is initiated and controlled by the central nervous system. Nervous signals initiate contraction of the respiratory muscles which act on the lungs and thorax to produce ventilation.

Animal studies which initially involved destruction of specific areas of brain have provided information about the regulation of respiration which has been applied to man. Because of the obvious difficulties with human research in this area, a great deal of the information from animal studies has not been substantiated in man although the evidence available indicates that similar control mechanisms exist.

It is convenient to think of the neurons which are involved in the control of respiration as the respiratory center. This designation is a physiologic one as these cells are widely scattered in the brainstem. Legallois (77) in 1824 located the respiratory center in the medulla oblongata. It was well recognized at that time that sections through the brain at any level rostral to the upper border of the pons had little effect on respiration while sections at lower levels produced a variety of changes. A section candal to the tip of the calamus scriptorius produced cessation of respiration. Since then work by Markwald in 1887, Lumsden in 1932 and others have resulted in our present concept of how the respiratory center controls respiration.

The respiratory center (35) is composed of collections of neurons which control the respiratory motor neurons located at lower levels in the central nervous system which activate the respiratory muscles to produce pulmonary ventilation. The respiratory center is composed of neurons whose activity is primarily inspiratory or expiratory in nature and are located in the lower medulla. Connections from these inspiratory neurons in the medulla go to another group of neurons called the pneumotaxic center which is located in the upper part of the pons. The pneumotaxic center has connections and controls another group of neurons called the apneustic center. The apneustic center directly influences the inspiratory center. This autoregulation of the inspiratory center converts constant inspiratory excitation into rhythmical bursts of activity which activate the respiratory

motor neurons. In addition to this autoregulation, the inspiratory center is influenced by signals from higher nervous centers. These higher centers produce voluntary control and integrate respiration during complex involuntary activities such as laughing, crying, etc. The activity of the respiratory center is also modified by signals from peripheral baro-, chemo- and pulmonary stretch receptors.

The respiratory center controls ventilation by integrating all the stimuli it receives with its own inherent activity to regulate the lower motor neurons which activate the respiratory muscles to produce the required ventilation.

C. THE CHEMICAL CONTROL OF RESPIRATION

Man has long known of the changes in respiration which occur with different activities and illnesses. Their significance and manner of production however were not understood until relatively recently. The discovery of oxygen by Priestley, Schaele and Lavoisier between 1775-7 was a significant finding. When Lavoisier showed that breathing was important to supply oxygen to the body rational research in pulmonary physiology had begun.

Early in the nineteenth century, the control of breathing by neurons in the brainstem had been well established and several theories had been proposed by various investigators to explain the control mechanisms involved. In 1885, the German physiologist Miescher-Rusch (67) discussed the various theories and concluded that carbon dioxide and not oxygen should be considered the humoral stimulus for respiration, although he felt that oxygen at low concentrations may play a role.

Haldane and Priestley (58) in 1905 demonstrated the role of carbon dioxide in the control of ventilation. In two subsequent papers, Douglas and Haldane (68) and Boycott and Haldane (59) showed that carbon dioxide alone could not fully explain the ventilation produced by exercise. They concluded that arterial acidity and not molecular carbon dioxide was the prime stimulus to ventilation. Winterstein (61) believed that hydrogen ion was the only stimulus to ventilation but he could not explain the increased ventilation which accompanied low alveolar oxygen pressures and normal or decreased blood acidity. For these same reasons, Haldane and co-workers (59, 68) reasoned that anoxaemia must be a stimulus to ventilation separate from blood acidity.

Jacob in 1920 (60) showed that CO_2 penetrated the cells and formed intracellular acid. This observation was used by Gessell (62) who proposed the concept that intracellular acidity of the respiratory neurons rather than acidity of the arterial blood was responsible for the control of respiration. In 1936, Nielsen (64) attempted to resolve the dispute about the common or independant roles of carbon dioxide and hydrogen ion as respiratory stimuli. He gave his subjects ammonium chloride for several days to produce a metabolic acidosis. During this period of increased acidity, the ventilation was only slightly increased. However, the threshold level necessary for

carbon dioxide to increase ventilation further was considerably lowered. In another part of this study, Nielsen's subject lived for several days in an atmosphere which contained increased carbon dioxide. Although the acidity of arterial blood was lower than when the metabolic acidosis had been produced by ammonium chloride, the pulmonary ventilation was greatly increased for the total period of carbon dioxide breathing. He concluded that this was conclusive evidence that hydrogen ion and carbon dioxide stimulated respiration independently.

This controversy has continued following Nielsen's studies. Leusen (69, 70, 71) demonstrated that acute experimental respiratory acidosis or alkalosis in dogs was rapidly followed by similar changes in the cerebrospinal fluid, but the production of a marked metabolic acidosis or alkalosis by the infusion of ammonium chloride, lactic acid, hydrochloric acid, sodium bicarbonate and disodium carbonate produced little change in the cerebrospinal fluid hydrogen ion content. The small changes in hydrogen ion content produced were in a direction opposite to the shifts measured in arterial blood hydrogen ion. This observation has been substantiated by other investigators (72). These studies demonstrated that intracellular hydrogen ion is the central stimulator to respiration and arterial carbon dioxide is a more potent stimulator than arterial hydrogen ion only because it gets into the cerebrospinal fluid more readily.

The role of hypoxia as a stimulus to ventilation separate from hydrogen ion as proposed by Miescher-Rusch (67) and Haldane and co-workers (59, 63, 69) was resolved by the discovery of the peripheral chemoreceptors in the carotid body and aortic arch by Heymans and Heymans in 1926 (65, 66). Subsequent studies have shown that these receptors are totally responsible for the hypoxic drive to breathe and partially responsible for the ventilatory response to carbon dioxide.

Exercise produces an increase in ventilation which is much larger than can be explained by the known chemical stimuli. It would appear that all the mechanisms involved in the ventilatory response to exercise have yet to be determined.

D. THE RESPIRATORY SYSTEM, ITS RESISTANCES AND TOTAL WORK OF BREATHING

When the inspiratory center generates a signal, it is transmitted to the inspiratory muscles by the phrenic and intercostal nerves. If the signal is above their threshhold level, these muscles contract and do measureable amounts of work. This amount of work is required to overcome the mechanical resistances to breathing and produce air flow. These resistances in the pulmonary system may be separated topographically into those related to A. the airways, B. the lung parenchyma, and C. the chest wall, which is considered to include the thorax, pleural space, and the abdomen. These resistances have also been separated on a physiological basis into A. elastic and B. non-elastic, which includes tissue viscous resistances and airway resistance.

In order to understand the factors which influence the conversion of respiratory muscular contraction into useful work, the physical properties of the lungs and thorax must be studied in addition to muscle physiology.

In addition to the neurological areas previously discussed, the respiratory system is composed of the lungs and chest wall. The chest wall is a rigid funnel shaped structure (larger at the bottom), which tends to resist changes in size and shape. It is composed of twelve pairs of bony ribs which articulate with the twelve thoracic vertebrae posteriorly and with the manibruim and sternum anteriorly. Completely lining the inside of this cavity is a thin membrane called the parietal pleura which is pain sensitive.

The spaces between the ribs are completely covered with muscles, tendons, connective tissue and skin. The funnel is closed at the upper end by the muscles, connective tissue, bones and skin of the neck and at the lower end it is separated from the abdomen by the large domed shaped muscular diaphragm. This muscle is the major muscle of respiration and is innervated by the bilateral phrenic nerves. The diaphragm is a striated muscle which is attached to the vertebrae, lower ribs and sternum at its periphery, and to the mediastinum centrally. Because of its usual domed shape, contraction produces a flattening of the dome with a consequent increase in the intra thoracic volume and decrease in the intra thoracic pressure. The intercostal muscles innervated bilaterally by the segmental intercostal nerves also increase the intra thoracic volume

and decrease the intra thoracic pressure when stimulated. This is accomplished because the ribs articulate with the vertebrae posteriorly which are fixed to form a pivot and with the manubrium and sternum which are free to move. As the intercostals contract, the ribs are moved outwards and superiorly to increase the intra thoracic volume and decrease the intra thoracic pressure. This decrease in intra thoracic pressure relative to the atmosphere forces air to enter the airways when in free communication with the atmosphere. The accessory muscles of respiration are not used normally, but when required, they help with pulmonary ventilation. The sternomastoids which arise from the cervical vertebrae and attach to the manibrium increases the intra thoracic volume by elevating the whole chest cage which further pivots the ribs posteriorly on the thoracic vertebrae. The trapezius stabalizes the arms and allows the pectoral muscles to assist pulmonary ventilation.

The chest wall is resistant to change in shape because of its elastic properties. Most of the work done on the chest wall to change lung volume is elastic in nature with a small amount of tissue viscous work. Elastic work in the respiratory system is the work done to produce a change in size and shape of the system. The amount of work done is not dependent upon the rate at which the work was done, but is determined by the amount of change which took place and the lung volume from which the work began. An important characteristic of inspired elastic work is that most of it is stored as energy which may be recaptured. This recapture occurs during expiration when the elastic recoil of the lungs and chest wall usually is sufficient to emphy the lungs without any muscular contraction.

The second form of work done on the chest wall is tissue viscous work. This occurs when the tissues actually slip relative to each other rather than just deform. This amount of resistance has been measured by Mead (31) who felt it to be insignificant when compared to the other respiratory resistances. In disease states, the normal elastic properties of the chest wall may be markedly altered. A common example is ankylosing spondylitis. In this form of arthritis, the articulating joints between the thoracic vertebrae, ribs, manubrium and sternum become fixed. The rigid nature of the chest wall requires very large amounts of work to deform it. Because this large amount of work is not acceptable, these patients usually become totally dependent upon diaphragmatic movement to produce pulmonary ventilation.

The lungs are the organs of respiration in which air and blood come into intimate contact. All the work done is to provide enough pulmonary ventilation to oxygenate the blood fully and remove the carbon dioxide produced by cellular metabolism. The lungs may be thought of as a network of branching hollow tubes connected to the atmosphere and surrounded by the parenchyma. The parenchyma is a loose framework of elastic, collagen and reticular fibrils in which the vascular bed and large numbers of cells and interstitial fluid are found. Fissures and fibrous bands divide the lung into lobes and segments. These segments are more completely separated in animals other than man and follow the subdivision of the airways. The parenchyma is completely covered by a thin, glistening membrane termed the visceral pleura which is continuous with the parietal pleura at the roots or hila of the lungs. The parietal and visceral pleura are normally in close contact, separated only by a very thin layer of fluid and cells.

In the lung, there are three types of resistances which must be overcome by the respiratory muscles to produce pulmonary ventilation. They are

A. Airway Resistance
B. Elestic resistance
C. Tissue viscous resistance

The elastic and tissue viscous resistances in the lung have the same characteristics as in the chest wall previously discussed. Work done to overcome non-elastic resistance is dissipated in the form of heat and must be done during both inspiration and expiration. The amount of work done is dependent not only on the amount of resistance in the airways, but also on the rate at which the work is done. If the flow rate is increased, the amount of work required to overcome the airway resistance is larger than if the same volume of gas is ventilated at a slower flow rate.

Because it is technically difficult to directly measure the total pressure generated by the respiratory muscles to overcome the resistance in the chest wall and lung, the total work of ventilation has been indirectly measured in several ways. Otis et al (83) measured the total work of breathing in trained subjects who were relaxed and ventilated by a Drinker respirator. Subsequently Butler (56) studied the work of breathing in patients who were anaesthatized and curarized. Butler's measurements were significantly greater than those of Otis et al, but subsequently Butler and Smith (57) demonstrated that pulmonary resistance increases during anaesthesia.

Campbell et al (26) and Cherniack (27) used a metabolic method to determine the total work of breathing. In these studies, the metabolic cost (oxygen cost) of increasing ventilation was measured at between 0.3 and 1.8 mls. of oxygen per litre of ventilation. Cherniack (27) also demonstrated that the oxygen cost of ventilation is elevated between four and ten times above the normal values in patients with emphysema.

E. THE MUSCLES OF RESPIRATION

The muscles which normally take part in respiration are the diaphragm and the intercostal muscles. When the need arises, other muscles such as the sternomastoids, abdominal, scaleni, trapezius, pectoralis major and minor and latissimus dorsi have all been found to contribute to ventilation and are collectively termed the accessory muscles of respiration.

The respiratory muscles are striated muscles (84) similar to other striated muscles in the body. They have been differentiated into red or white muscles depending upon the relative amounts of sarcoplasm, mitochondria, fat droplets and myoglobin which are more abundent in the red muscles (84). Within each muscle mass there are fibers which may be designated as red, white or intermediate by histological and histochemical analysis.

The activation of the respiratory muscles is similar to other striated muscles. Katz (49) states that the arrival of a nerve impulse at the neuromuscular junction causes the release of acetyl-choline from the nerve ending. Acetyl-choline diffuses across the myo-neural junction to the muscle side where it produces a change in the end plate potential. This change in potential gives rise to a spreading wave of depolarization along the surface membrane of the muscle fibre which allows mass ionic exchange across the membrane and activation of the contractile proteins which shorten and produce work.

The physiology of the respiratory muscles has been intensively studied and compared to other striated muscles.

Creese et al (85) have shown that in a resting (porarized) state an electrical potential of -80 mv. exists across the membrane of human intercostal muscles which is similar to other striated muscles.

When stimulated, all muscles don't contract at the same speed. On this basis, they have been divided into fast and slow muscles. Buller et al (86, 87) have demonstrated that this difference is not related to the muscle itself but rather to the nervous control it receives. By transferring the nerves of fast and slow muscles, they changed the characteristics of the muscles to correspond to

that of the nerve implanted. Fast and slow fibres have been demonstrated by Hofman et al (88) in biopsy specimens of human intercostal muscles.

Evans and Hill (103) demonstrated that the maximum tension developed by a muscle when stimulated depends upon its initial length. Each muscle has an optimum length for contraction, and any change in its length alters the tension that it can develop . The relationship between the force of muscular contraction and the velocity of muscle shortening has been described by Hill's classical equation--

$$(P+a)(V+b) = (Po+a)b$$

P = force at velocity V
Po = force at velocity zero
a = constant with dimensions of force
b = constant with dimensions of velocity

Hill (90) has noted that the maximum power occurs at about 0.3 times the maximum speed and about 0.3 times the maximum load. The observation by Rahn et al (42) that the maximum inspiratory pressures generated by the respiratory system are at the lowest lung volumes and progressively decrease at higher lung volume and that maximum expiratory pressures are generated at TLC and progressively diminish at lower lung volumes has been confirmed by other investigators (39, 40, 53). This would indicate that the optimum position for contraction of the inspiratory muscles is at least at residual volume and may even be lower. Changes in the end tidal level of the respiratory system appear to change the length:tension relationship of the respiratory muscles which generates the pressures.

In addition to information about the pressures generated by the inspiratory muscles at different lung volumes, Agostoni et al (91) studied the differences in the shape of the thorax produced by contraction of the respiratory muscles. The measured differences in the shape of the thorax in subjects who maintain the same lung volume by active muscular contraction with their glottis open and with muscular relaxation against a closed glottis. They demonstrated that the inspiratory muscles produce a change in the shape of the thorax as well as changes in intra thoracic pressure and volume.

Although the role of the diaphragm as an inspiratory muscle has been accepted, the inspiratory activity of the intercostals has been in dispute. The function of the internal and external intercostal muscles in respiration has been resolved by Taylor (93) who used

bipolar electrodes to selectively record electrical activity of the intercostal muscles in humans during quiet respiration. He demonstrated that the external intercostal is an inspiratory muscle and the internal intercostal is expiratory except for its parasternal intercartilaginous part which acts as an inspiratory muscle.

In addition to a motor role, the muscles have long been known to contain sensory endings. Huber (92) in 1901 demonstrated the presence of muscle spindles, tendon organs and Pacinian corpuscles in the intercostal muscles of cats. Similar sensory organs were demonstrated in human respiratory muscles by Widdicombe (41) and by Winckler (94), who recorded action potentials in their afferent nerves. Although these sensory organs have been demonstrated in man, their exact role in the regulation of respiration in man is still unclear (43). However, information is available that indicates they do alter respiration in experimental situations.

Sears and Newsom-Davis (50) have shown that intercostal muscle proprioceptors produce a segmental reflex response in the intercostal muscles within the first loaded breath. This response, however, is brief and the effects are usually negligible.

The factors involved in interpretation of various added loads have been studied by Campbell et al (89) who have demonstrated that the addition of an elastic load of 2.5 cm. H_2O/L. or a resistive load of about 0.75 cm. H_2O/L./sec. can be perceived. They concluded that to perceive the load, a person must interprete that there is an alteration in the usual volume change that a pressure generated produces. The term length:tension inappropriateness was used to help explain this idea. Campbell and Howell (81) subsequently showed that resistive loads were more readily identified than were elastic loads.

Guz et al (47) studied the role of the vagal and glossopharyngeal afferent nerves in respiratory sensation and the control of breathing in man. In two normal subjects who had their vagal and glosso-pharyngeal nerves blocked by local anaesthetic drugs, no difference was found in their ability to detect added loads. Loads which were unpleasant before the block were reported to remain just as unpleasant.

They did observe significant changes in breath holding time. Doubling of the time to the breaking point at TLC was observed

and the usual distress which occurs close to the breaking point were alleviated. This evidence demonstrated that the receptors for the detection of added resistance don't reside in the lung. The receptors and pathways for some of the drive to breathe during breath holding are located in the lung and are mediated by the vagi and glossopharyngeal nerves. Campbell et al (95) showed that the receptors which produce distress during breath holding could be completely blocked by tubocurare as the sensation which occurs at the breaking point was never reached during their study. This evidence indicated that the respiratory muscles were involved in the distress which accompanies breath holding although the drive to breathe arises from lung receptors.

Pacinian corpuscles and free nerve endings have been demonstrated in the intercostal muscles and may detect pressure and pain sensations (48). Muscle spindles and tendon organs found in the intercostal muscles don't appear to be responsible for detecting the sensation of movement or resistance to movement of the chest wall (98). Studies to determine the pathways which detect added elastic and resistive loads have produced contradictory conclusions. Newsom-Davis (80) studied a group of patients who had upper spinal cord lesions which predominantly affected their ability to sense proprioception. In these spontaneously breathing patients, he found a gross impairment of their ability to detect added loads. He also studied the effects of sensations to passive movements of the chest wall. In one patient with a C3 cord transection which blocked afferent impulses from the chest wall the ability to determine chest movement was grossly impaired. A tracheostomized patient with polio used as a control patient had a normal ability to detect small changes in loads. Dispute arose in the literature because several investigators reported that patients with nervous system lesions similar to those studied by Newsom-Davis could detect increased resistive loads. Their conclusions were refuted by Newsom-Davis (80) who reasoned that these patients with normal sensation in the upper respiratory system were detecting oro-pharyngeal pressure changes and not the added elastic or resistive loads. He demonstrated a marked reduction in the ability of these patients to detect changes in respiratory loads following application of local anaesthetic drugs to the oro-pharynx. This evidence indicates that the ability to detect added elastic and resistive loads resides predominently in proprioceptive sensory endings which are located in the chest wall.

Campbell and Howell (43) demonstrated very rapid increases

in the force of contraction in response to various types of added work loads. This response appears much too rapid to be explained by any chemical changes in blood gas tensions. The pathway for this reflex is unknown however proprioceptors in the chest wall may be responsible. Howell (6) has shown a linear relationship exists between end tidal pCO_2 and inspiratory power for added elastic loads, however, the pathways for this reflex have not yet been determined. Milic-Emili and Tyler (9) have shown that at any alveolar pCO_2 tension, inspiratory work rate is independent of added or subracted loads. They attributed this to the force-velocity relationship of the respiratory muscles and concluded that the controlling mechanism acts to maintain a rate of work and not pulmonary ventilation in response to stimulation.

The observation by Rahn et al (42) that the maximum respiratory pressures generated are dependent upon lung volume have been confirmed by other investigators (29,32,39,40). The maximum pressures generated diminished as the end expiratory level increases. Cook et al (53) found that children could generate much higher pressures than could adults. They also noted that in addition to age and end tidal level, the maximum pressures generated also depended upon the thickness of the chest wall. According to the law of Laplace, the pressure exerted in a cylinder or sphere for a given tension of the wall is inversely proportional to the radius. The higher pressures generated by the children as compared to men appears to be related to the smaller radius of curvature of the rib cage, of the diaphragm and of the abdominal wall (40).

In animal studies, Wolding (36) has shown that when the inspiratory center is stimulated, the diaphragmatic activity decreases with increasing lung volumes. In a subsequent study, Stanley et al (23) demonstrated that integrated phrenic nerve activity was similarly altered by a change in lung volume. This evidence indicates that reflex inhibition which acts on the inspiratory center and is related to lung volume must be arising from the lungs.

From other animal experiments two Hering-Bruer reflexes both mediated through afferent vagal channels with opposite results have been demonstrated. One brought about by stimuli arising from stretch receptors in the lungs causes depression of centrally mediated inspirations; the other, brought about by deflation causes stimulation of centrally mediated inspiration. The afferent vagal

discharge for both reflexes is dependent on lung volume and independent of respiratory movement (19, 22).

In other animal experiments, it has been shown that if the vagi are intact, stimulation of respiration occurs when expansion of the chest is restricted by external chest pressure (45, 46, 44) or negative pressure breathing (37).

Mithoefer et al (52) suggested that both Hering-Bruer reflexes were operative in their experiments relating breath holding to lung volume. Lung inflation depressed and lung deflation stimulated breathing. The strength of the stimulation increased exponentially from maximum depression at the position of complete inflation of the lungs to maximum stimulation at forced expiration.

A positive interaction of neurogenic factors with carbon dioxide responsiveness was demonstrated by Scott (17) and by Richardson and Widdicombe (14). In two human subjects studied by Guz et al (47), the ventilatory response to carbon dioxide was diminished after local anesthetic block of the vagus and glossopharyngeal in the neck, suggesting that vagal impulses from the lungs are important in the maintenance of carbon dioxide sensitivity.

The evidence from all studies indicates that the relative position of the end tidal level and lung volume should be important in determining the amount of work done by the respiratory system when it is stimulated.

F. VENTILATORY RESPONSE TO CARBON DIOXIDE

Since 1905, when Haldane and Priestley (58) first demonstrated the role of carbon dioxide in the regulation of respiration, it has been extensively used to investigate the respiratory system. The observation by Reinhardt in 1912 (15) of a diminished ventilatory response to carbon dioxide by patients with pulmonary emphysema has been confirmed by others (2, 8, 9, 12, 13, 16, 18, 20, 28, 30, 38). The mechanism producing this reduction has been investigated, but has not been resolved. Scott (16), Donald and Christie (18) and others (13, 20) felt that the delay in response to carbon dioxide seen in patients who were hypercapnic was due to the increased bicarbonate of their blood. Tenney (28) disagreed and stated that a true respiratory center depression existed in patients with a diminished ventilatory response to carbon dioxide. He felt that relationship existed between the degree of pre-existing carbon dioxide retention and the change in the response curve. Other investigators (12, 32, 33) agreed with Tenney, although Flenley (32) felt that part of the reduction could not be explained by a depressed respiratory center or increased buffering capacity of the blood.

In 1956, Cherniack and Snidal (4) first demonstrated that the diminished response to carbon dioxide could be reproduced in normal subjects by breathing through an external non-elastic resistance. They showed that improvement in the ventilatory response to carbon dioxide could be produced in patients with airway obstruction by reduction of the airway resistance with bronchodilators. This indicated that alteration in the normal resistances of the respiratory system and not necessarily a depressed respiratory center could explain the reduction seen in most patients. These observations have since been confirmed by other investigators (1, 3, 5, 6, 7, 24, 29). Because Shafer (25) stated that long term exposure to elevated inspired carbon dioxide leads to a reduced ventilatory response to further carbon dioxide increases, Zechman et al (24) proved that this did not occur in the normal subjects breathing with added non-elastic resistance they studied because the ventilatory response to carbon dioxide was normal after breathing carbon dioxide for a similar time period without resistance. Wood and Barnett (11) also improved the response in patients with airway obstruction by substituting helium for nitrogen in the respired gas mixtures. This substitution reduced the non-elastic resistance without otherwise altering the respiratory system. These studies indicate that

in most subjects, the reduction in the ventilatory response to carbon dioxide is related to the resistances in the lungs and can be altered by manipulating these resistances. In spite of the reduced ventilatory response to carbon dioxide, Richards et al (21) found that when the responses were expressed in terms of the oxygen cost of breathing, the response in four patients with emphysema was normal. This would indicate that the work done by these patients is correct for the afferent impulses received by the respiratory center. Other studies were carried out to assess the stimulation received by the respiratory muscles. Lourenco et al (8) measured the response to carbon dioxide in patients with chronic obstructive lung disease in terms of the integrated diaphragmatic electromyograms. They found that obstructed patients who were not hypercapnic had a normal response whereas patients who were hypercapnic had a diminished response. They concluded that the diminished ventilatory response to carbon dioxide in most patients was due to mechanical factors related to the lungs and thorax, but in those patients who were hypercapnic, a true depression of the respiratory center was often present. Fritts et al (34) measured the work done in response to an increase in arterial pCO_2 in four patients with emphysema compared to normal controls and found that the increase in mechanical work in response to an increase in arterial pCO_2 was the same even though the ventilatory response was depressed in the four patients with emphysema. They concluded that a disturbance in mechanics alone could account for the diminished ventilatory response to carbon dioxide in some patients with emphysema. From all of these studies, it would appear that there is sufficient evidence to accept the hypothesis that most patients with a diminished ventilatory response to carbon dioxide, exclusive of those who are hypercapnic, have a normal respiratory center which probably regulates pulmonary work and not ventilation.

Panchenko (38) studied the carbon dioxide sensitivity of the respiratory center in patients with chronic hypercapnia. He gave five or six percent carbon dioxide to patients with emphysema and recorded their minute volumes and bioelectric potentials from the respiratory muscles. Sharp increases in electrical activity of the respiratory muscles and diminished respiratory responses to inhaled carbon dioxide were seen. He concluded that the diminished ventilatory response to carbon dioxide was the result of an alteration of the peripheral respiratory system rather than a depression of the respiratory center. If his results are confirmed, it would mean that the diminished ventilatory response to carbon dioxide seen in obstructed patients with hypercapnia also is the result of mecahnical

factors and true depression of the respiratory center in these patients is rare.

In addition to the alteration in the ventilatory response produced by added resistance to breathing, investigations have been carried out to evaluate separately the factors which comprise the minute ventilation in an effort to determine how and where the various mechanisms operate.

Rohrer (55) suggested that an optimum pattern of respiration is based on the minimum work of breathing. The slow deep breaths which occur with increased non-elastic resistance and the rapid shallow respirations associated with a high elastic resistance conforms to this suggestion. Mead (82) while studying guinea pigs concluded that minimum work was not the signal as Rohrer had predicted, but that mimimum inspiratory force was. Both McIlroy et al (29) and Cain and Otis (3) felt that in addition to the rate and frequency being important, the end tidal level was also significant in arriving at a pattern of respiration in response to added elastic and non-elastic resistances.

The effects of elastic loading on the respiratory pattern and minute ventilation have been investigated. Milic-Emili and Tyler (9) reported a marked change in tidal volume with little or no change in the end tidal level following inspiratory elastic loading. They found the rate of work/breath and the total work/breath the same as in the unloaded state and concluded that the controlling mechanism maintains a given rate of work and not ventilation. Howell (6) has shown that the ventilatory response to carbon dioxide in normal subjects breathing with an increased elastic resistance is normal although the frequency and tidal volume were altered. This observation has been confirmed by Cherniack and Levison (73).

In addition to the response to added elastic and non-elastic resistance, the effects produced by positive and negative pressure breathing are of considerable interest. Rahn et al (42) and others (78, 79) have shown that with prolonged pressure breathing, the end tidal level no longer followed the relaxation pressure volume curve. Both the tidal volume and end tidal level fell below the curve with positive intra-pulmonary pressures up to 30 cm. H_2O. The application of pressure to the respiratory system of man usually produces an immediate change in the end tidal level and tidal volume as demonstrated

by Rahn and co-workers (42) and Widdicombe (41). Naimark and Cherniack (75) have demonstrated that the respiratory muscles are relaxed at the end tidal level during pressure breathing in man so that muscular activity does not account for the change. Because these changes in lung volume have a profound effect on the compliance and flow-resistances within the lung it is to be expected that a change in end tidal level will alter ventilation significantly in its response to stimulation.

Flenley and co-workers (32) have shown that the immediate effects of the respiratory system to positive pressure breathing is to alter the end-tidal level and tidal volume. They found that as the intra-pulmonary pressures became more positive, the tidal volumes decreased. At negative intra-pulmonary pressures up to -10 cm. H_2O, the tidal volumes increased slightly but with further increases in negative pressures, the tidal volumes fell. They interpreted this observation to indicate significant increases in the internal resistances at low lung volumes.

In contrast to the previously described studies of normal subjects using positive and negative pressure breathing. Tyler and Grape (74) studied the ventilatory response to carbon dioxide in patients with emphysema and normal control subjects using a servo-controlled patient cycled respirator. In the control subjects after an initial transient hyperventilation, six of the seven subjects returned to their normal minute ventilation and $PaCO_2$ levels. In contrast, the emphysematous patients maintained higher minute ventilations in six of the eight patients studied and lowered their $PaCO_2$ while breathing ambient air. The introduction of a carbon dioxide enriched mixture to return their $PaCO_2$ to the unassisted resting level produced a significant increase in their minute ventilations.

All of these studies indicate that these patients have normal respiratory control mechanisms, but that hypercapnia is a result of an inability of the respiratory apparatus to produce the required ventilation.

Alteration in the end tidal level produces tremendous changes in the internal resistances and the mechanical relationship of the respiratory muscles to the thorax. It would appear from the evidence to date that the position of the end tidal level could be important in the ventilatory response to stimulation.

G. SUMMARY

The addition of an external airway resistance leads to a reduction in the ventilatory response to carbon dioxide while a reduction in airway resistance leads to an improvement in the ventilatory response. Thus it has been suggested that an increased work of breathing may limit the ventilatory response. On the other hand, an increased work of breathing due to added elastance does not influence the ventilatory response to carbon dioxide. Since it has been shown that the ventilatory response to carbon dioxide is diminished when the lung volume is increased or with positive pressure breathing which increases lung volume, it is possible that the diminished response to carbon dioxide with added external non-elastic resistance is related to the increase in resting level or lung volume which accompanies this situation. In Part II of this thesis are reported the results of studies carried out to determine if the diminished response to carbon dioxide during resistive loading could be attributed to the increase in lung volume which occurs in this situation.

H. BIBLIOGRAPHY

1. Barnett, T.B., and B. Rasmussen: Ventilatory responses to hypoxia and hypercapnia with external airway resistance. Acta Physiol. Scand. 80: 538-551, 1970.

2. Brodovsky, D., J.A. MacDonnell, and R.M. Cherniack: The respiratory response to carbon dioxide in health and emphysema. J. Clin. Invest. 39: 724-729, 1960.

3. Cain, C.C., and A.B. Otis: Some physiological effects resulting from added resistance to respiration. J. Aviation Med. 20: 303-308, 1957.

4. Cherniack, R.M., and D.P. Snidal: The effect of obstruction to breathing on the ventilatory response to CO_2. J. Clin. Invest. 35: 1286-1290, 1956.

5. Eldridge, R., and J.M. Davis: Effect of mechanical factors on respiratory work and ventilatory responses to CO_2. J. Appl. Physiol. 14: 721-726, 1959.

6. Howell, J.B.L.: Breathlessness in pulmonary disease. In Breathlessness. Blackwell Scientific, Oxford, 165-177, 1966.

7. Kellogg, R.H., D.E. Leith, and K. Konno: Ventilatory response to CO_2 when respiratory resistance and elastance are reduced in normal subjects. Fed. Proc. 23: 259, 1964.

8. Laurenco, R.V., and J.M. Miranda: Drive and performance of the ventilatory apparatus in chronic obstructive lung disease. New Eng. J. Med. 279: 53-59, 1968.

9. Milic-Emili, J., and J.M. Tyler: Relationship between $P_{A_{CO_2}}$ and respiratory work during external resistance breathing in man. Ann. N.Y. Acad. Sci. 109: 908-914, 1963.

10. Riley, R.L.: The work of breathing and its relation to respiratory acidosis. Ann. Int. Med. 41: 172-176, 1954.

11. Wood, W.B., and T.B. Barnett: Effects of helium mixtures on ventilatory response to CO_2 in subjects with airway obstruction. Clin. Res. 8: 77, 1965.

12. Fishman, A.P., P. Samet, A. Cournand: Ventiltory drive in chronic pulmonary emphysema. Am. J. Med. 19: 533, 1955.

13. Alexander, J.K., J.R. West, J.A. Wood, and D.W. Richards: Analysis of the respiratory response to carbon dioxide inhalation in varying clinical states of hypercapnia, anoxia and acid-base derangement. J. Clin. Invest. 34::511, 1955.

14. Adrian, E.D.: Afferent impulses in the vagus and their effect on respiration. J. Physiol. 79: 332-358, 1933.

15. Reinhardt, R.: Uber das Verhattnis von CO_2-auscherdring zur alemgrosse beim lungenemphysema. Deutsches Arch. Klin. Med. 109: 192, 1912.

16. Scott, R.W.: Observations on pathologic physiology of chronic pulmonary emphysema. Arch. Int. Med. 26: 544, 1920.

17. Scott, F.H.: On the relative parts played by nervous and chemical factors in the regulation of respiration. J. Physiol. (Lond.) 301-326, 1908.

18. Donald, K.W., and R.V. Christie: The respiratory response to carbon dioxide and anoxia in emphysema. Clin. Sci. 8: 33, 1949.

19. Larrabee, M.G., and G.C. Knowlton: Excitation and inhibition of phrenic motorneurons by inflation of the lungs. Am. J. Physiol. 147: 90-99, 1946.

20. Prime, F.J., and E.K. Westlake: The respiratory response to CO_2 in emphysema. Clin. Sci. 13: 321, 1954.

21. Richards, D.W., H.W. Fritts, and A.L. Davis: Observations on the control of breathing in emphysema: The effects of oxygen on ventilatory response to CO_2 inhalation. Tr. A. Am. Physicians, 71: 142, 1958.

22. Adrian, E.D.: Afferent impulses in the vagus and their effect on respiration. J. Physiol. 79: 332-358, 1933.

23. Stanley, N.N., P.G. Tuleur, M.D. Altose, and N.S. Cherniack: Interaction of lung volume and chemical stimuli on respiratory drive. Fed. Proc. 31: 815, 1972.

24. Zechman, R., F.G. Hall, and W.E. Hull: Effects of graded resistance to tracheal air flow. J. Appl. Physiol. 10: 356-362, 1957.

25. Schafer, K.E.: Atmung und Saure-Basengleichgewicht bei langdauernden aufenthalt in 3% CO_2. Pfluger's Arch. ges. Physiol. 251: 689, 1949.

26. Campbell, E.J.M., Westlake, E.K., and Cherniack, R.M.: Simple methods for estimating oxygen consumption and efficiency of the muscles of breathing. J. Appl. Physiol. 11: 303, 1957.

27. Cherniack, R.M.: The oxygen consumption and efficiency of the respiratory muscles in health and emphysema. J. Clin. Invest. 38, 494-499, 1959.

28. Tenney, S.M.: Ventilatory response to carbon dioxide in pulmonary emphysema. J. Appl. Physiol. 6: 477, 1954.

29. McIlroy, M.D., F.L. Eldridge, J.P. Thomas and R.V. Christie: The effects of added elastic and non-elastic resistances on the pattern of breathing in normal subjects. Clin. Sci. 15: 2, 337-344, 1956.

30. Flenley, D.C., and J.S. Millar: Ventilatory response to oxygen and carbon dioxide in chronic respiratory failure. Clin. Sci. 33: 319-334, 1967.

31. Mead, J.: Measurement of inertia of the lungs at increased ambient pressure. J. Appl. Physiol. 9: 208, 1956.

32. Flenley, D.C., L.D. Pengelly, and J.Milic-Emili: Immediate effects of positive pressure breathing on the ventilatory response to CO_2. J. Appl. Physiol. 30: 1, 7-11, 1971.

33. Pevny, E., and N. Scheida: Tolerance curves of carbon dioxide during rebreathing in normal subjects, pulmonary emphysema and obesity. Dis. Chest. 53: 470-475, 1968.

34. Fritts, H.W., Jr., A.P. Fishman, A. Cournand: Factors contributing to the diminished ventilatory response to CO_2 of patients with obstructive emphysema. Fed. Proc. 16: 178, 1957.

35. Cherniack, R.M., L. Cherniack and A. Naimark: The Control of Breathing. In Respiration in Health and Disease, Second Edition, W. B. Saunders Company, Philadelphia. 103-116, 1972.

36. Woldring, S: Interrelationship between lung volume, arterial CO_2 tension and respiratory activity. J. Appl. Physiol. 20: 647-652, 1965.

37. Culver, G.A., and H. Rahn: Reflex respiratory stimulation by chest compression in dogs. Am. J. Physiol. 168: 686-693, 1952.

38. Panchenko, I.A.: Carbon dioxide sensitivity of the respiratory centre in chronic hypercapnia. Bull. Exper. Biol. Med. 49: 444, 1960.

39. Marshall, R: Relationships between stimulus and work of breathing at different lung volumes. J. Appl. Physiol. 17: 917-921, 1962.

40. Agostoni, E. and J. Mead: Statics of the respiratory system. Handbook of Physiol. Sec 3, 1: 387-409 Washington, D.C. Amer. Physiol. Soc., 1964.

41. Widdicombe, J.G.: Respiratory reflexes. Handbook of Physiol. Sec 3, 1: 585-630, Washington, D.C., Amer. Phys. Soc., 1964.

42. Rahn, H., A.B., Otis, L.E. Chadwick and W.O. Fenn: The pressure volume diagram of the Thorax and lung. Amer. J. Physiol. 146: 161-178, 1946.

43. Campbell, E.J.M., J.B.L. Howell: Proprioceptive control of Breathing. Ciba Foundation Symposium. Pulmonary Structure and Function. Little Brown, Boston, 403, 1962.

44. Gessell, R., and C. Moyer: Propriceptive reflex effects arising from deformations in the lungs and torso. Am. J. Physiol. 133: 293, 1941.

45. Hammouda, M. and W. H. Wilson: Vagus influence giving rise to phenomena accompanying expansion and collapse of lungs. J. Appl. Physiol. 74: 81, 1932.

46. Bakos, A.C.P. and W.L. Howell: Constriction of the mid-Thorax as a means of reflex maintenance of respiration during Barbiturate narcosis. Science. 108: 45-46, 1948.

47. Guz, A.M., M.I.M. Noble, J.G. Widdicombe, D. Trenchard, W.W. Mukin and A.R. Makay: The role of vagal and glosso-pharyngeal afferent nerves in respiratory sensation, control of breathing and arterial pressure regulation in conscious man. Clin. Sci. 30: 161-170, 1966.

48. Paintel, A.S.: Functional Analysis of group III afferent fibres of mammolian muscles. J. Physiol. (Lond.) 152: 250-270, 1960.

49. Katz, B.: Nerve, Muscle and Synapse. (McGraw-Hill), New York, 1966.

50. Sears, T.A., J. Newsom Davis: The control of respiratory muscle during voluntary breathing. Ann. N.J. Acad. Sci. 155: 183-190, 1968.

51. Margaria, R., G. Milic-Emili, J. M. Petil and G. Cavagna: Appl. Physiol. 15: 354-358, 1960.

52. Mithoefer, J.C., C.D. Stevens, H.W. Ryder and J. McGuire: Lung volume, Restriction, Hypoxia and Hypercapnia as inter-related respiratory stimuli in normal man. J. Appl. Physiol. 5: 797-801, 1953.

53. Cook, C.D., J. Mead, M.M. Orzalesi: State volume pressure characteristics of the respiratory system during maximum efforts. J. Appl. Physiol. 19: 1016-1022, 1964.

54. Evan, E.L. and A. V Hill: Retation of length of tension developed and heat production on contraction in muscle. J. Physiol. (Lond.) 49: 10, 1914.

55. Rohrer, F. Physiologie de Alemberoegung. Hand. norm. path. Physiol. 2: 70, 1925.

56. Butler, J.: The Kinetic resistance of the relaxed respiratory system. Clin. Sci. 16: 491, 1957.

57. Butler, J. and B.H. Smith: Pressure volume relationships of the chest in the completely relaxed anaesthetized patient. Clin. Sc. 16:125, 1957.

58. Haldane, J.S., and J.G. Priestley: The regulation of the lung ventilation. J. Physiol. 32: 225-266, 1905.

59. Boycott, A.E., and J.S. Haldane: The effects of low atmospheric pressure on respiration. J. Physiol. 37: 355-377, 1908.

60. Jacob, M.H.: To what extent are physiologic effects of carbon dioxide due to hydrogen ion. Am. J. Physiol. 51: 321-331, 1920.

61. Winterstein, H.: Die regulierung de almungdurch das blut. Zbl. Physiol. 24: 811, 1910.

62. Gessell, R.: On the chemical regulation of respiration. The regulation of respiration with special reference to the metabolism of the respiratory center. Amer. J. Physiol. 66: 5-49, 1923.

63. Haldane, J.S., A.M. Keilas, E.L. Kennaway: Experiments on acclimatization reduced atmospheric pressure. J. Physiol. 58: 181-206, 1920.

64. Nielsen, M.: Unlersuchunger uber die alemregulation bein menschen. Skand. Arch. Physiol. 74: Suppl. 10: 83-208, 1936.

65. Heymans, J.F., C. Heymans: Recherches physiologiques et pharmaco-dynamiques sur la tete isolee du chien. Arch. Int. Pharmacodyne, 32: 9-41, 1926.

66. Heymans, C.J., J. Bouckaert and P. Tegniers: Le sinus carotidien et la zone homoloque cardio-aortique. (Paris). Doin et Cie, 1933.

67. Miescher-Rusch, F.: Bemerkimgen zur lehre von den alhembewegunzen. Arch. Anal. Physiol. Lipz, 3: 355-380, 1885.

68. Haldane, J.B., and G.G. Douglas: The regulation of normal breathing. J. Physiol. 38: 420-440, 1909.

69. Leusen, I.R.: Influence du pH du liquide cephalo-rechidien sur la respiration. Experientia, 6: 275, 1950.

70. Leusen, I.R.: Acid base equilibrium between blood and cerebrospinal fluid. Amer. J. Physiol. 176: 513-6, 1954.

71. DeBersaques, J. and I.R. Leusen: Acid base equilibrium between blood and cerebrospinal fluid. J. Physiol. 126:14, 1954.

72. Cherniack, R.M., L. Cherniack, A. Naimark, In: Respiration in Health and Disease, Second Edition, W. B. Saunders Company, Philadelphia, 18-30, 1972.

73. Cherniack, R.M. and H. Levison: Influence of mechanical resistances on ventilatory response to hypercapnia and hypoxia: In press, 1972.

74. Tyler, J.M., and B. Grape: The influence on mechanical assistance to respiration on the ventilatory response to Carbon Dioxide in emphysema. American Rev. Resp. Dis. 86: 29-36, 1962.

75. Naimark, A., and R. M. Cherniack: Compliance of the respiratory system and its components in health and obesity. J. Appl. Physiol. 15: 377-382, 1960.

76. Pengelly, L.D., M. Kangalee, B. Vadelaga, A. Tarshis, and E.J.M. Campbell: Effects of voluntary control of tidal volumes on the ventilatory response to CO_2 in man. Fed. Proc. 31:2, 810, 1972.

77. Youmans, W. B.: The control of Breathing. The Physiological Basis of medical practice, 7th edition. Williams, Wilkins Company, Baltimore, 488-505, 1961.

78. Agostoni, E: Diaphragm activity and theraco-abdominal mechanics during positive-pressure breathing. J. Appl. Physiol. 17: 215-220, 1962.

79. Ernsting, E: The physiology of pressure breathing. In: A Textbook of Aviation Physiology. (Oxford) Pergamon Press, 343-373, 1965.

80. Newsom-Davis, J.: Contribution of somatic receptors in the chest wall to detection of added inspiratory airway resistance. Clin. Sci. 33: 249-260, 1967.

81. Campbell, E. J. M. and J. B. L. Howell: The sensation of breathlessness. British Med. Bull. 19: 36-40, 1963.

82. Mead, J.: Control of Respiratory Frequency. J. Appl. Physiol. 15: 325, 1960.

83. Otis, A. B., W. O. Fenn and R. Rahn: Mechanics of Breathing in man. J. Appl. Physiol. 2: 592, 1950.

84. Padykula, H. A. and G. F. Gauthier. Morphological and cytochemical characteristics of fibre types in normal mammalian sketal muscle, in: Exploratory Concepts in Muscular Dystrophy and Related Disorders, Excerpta. Medica Foundation: Inter Congr. Series: 147, 117-128, 1967.

85. Creese, R., J. B. Dillon, J. Marshall, P. B. Sabawala, D. J. Schneider, D. B. Taylor, D. E. Zinn: The effects of neuro-muscular blocking agents on isolated human intercostal muscles. J. Pharmacol. exp. ther. 119: 485-494, 1957.

86. Buller, A. J., J C. Eccles and R. M. Eccles: Differentiation of fast and slow muscles in the cat hind limb. J. Physiol (Lond.) 150: 399-416, 1960.

87. Buller, A. J., J. C. Eccles and R. M. Eccles: Interactions between motorneurons and muscles in respect of the characteristic speeds of their responses. J. Physiol. (Lond.) 150: 417-439, 1960.

88. Hoffman, W. W., W. Alston, and G. Rowe: A study of individual neuromuscular junctions in mytonia. Electroenceph. Clin. Neurophysiol. 21: 521-537, 1966.

89. Campbell, E. J. M., S. Freedman, P. S. Smith and M. E. Taylor: The ability of man to detect added elastic loads to breathing. Clin. Sci. 20: 223-231, 1961.

90. Hill, A.V.: The dimensions of animals and their muscular dynamics. Sci. Progr. 38: 209-230, 1950.

91. Agostoni, E., P. Magnoni, G. Torri and F. Sacacino: Relation between changes of rib cage circumfrence and lung volume. J Appl. Physiol. 20:1179-1186, 1965.

92. Huber, G.C.: Neuromuscular spindles in the intercostal muscles of the cat. Amer. J.Anat. 1: 520-521, 1901.

93. Taylor, A.: The contribution of the intercostals to the effort of respiration in man. J. Physiol. (Lond.) 151: 390-402,1960.

94. Winckler, G. and B. Delaloye: A propos de la presence de fuseaux neuromusculaires dans le diaphragme humaine. Acta. Anat. 29: 114, 1957.

95. Clark, T.J.H., B. G. Clarke, and J.M.B. Hughes: A simple technique for measuring changes in ventilatory response to Carbon Dioxide. The Lancet. 2: 368-371, 1966.

96. Campbell, E.J.M., S.Godfrey, T.J.H. Clark, S. Freedman, and J. Norman: The effects of muscular paralysis induced by tubocurarine on the duration and sensation of breath holding during hypercapnia. Clin. Sci., 36: 323-328, 1969.

PART II. RELATIONSHIP OF THE END-TIDAL LEVEL OF THE DIMINISHED VENTILATORY RESPONSE TO CO_2 DURING RESISTIVE LOADING IN NORMAL SUBJECTS

A. INTRODUCTION

Since the addition of an external resistance in normal individuals leads to a reduction in the ventilatory response to carbon dioxide (5, 6, 10, 15, 24) and a reduction in resistance leads to an improvement in ventilatory response (10, 22, 41), it has been suggested that an increased work of breathing may play an important role in limiting the ventilatory response to carbon dioxide. On the other hand, it has been demonstrated that an increased work of breathing due to the addition of external elastance does not influence the ventilatory response to carbon dioxide (9, 21, 29). This discrepancy between the effects of external resistance and elastic loading has not been adequately elucidated. A reduction in work done against internal elastic resistance during respiration, because of either lowering of end-expiratory level or smaller tidal volumes, and a difference in rate of work at a given pCO_2 in the two conditions have been suggested as possible mechanisms (21).

It has been shown that the ventilatory response to carbon dioxide is diminished when the lung volume is increased in animals (27, 40) or in humans (17) during positive pressure breathing which results in an increase in end-expiratory level. Since the end-expiratory level is increased with resistive loading but not with elastic loading (26), it is possible that the reduction in ventilatory response to carbon dioxide by added external resistance is related to an increase in end-expiratory level.

The purpose of this paper is to report the effect of changes in end-expiratory level on the ventilatory response to carbon dioxide during resistive loading.

B. METHODS

The ventilatory response to carbon dioxide was determined while resting and during external loading with resistances of 28.5 cm. H_2O/L./sec. and 36 cm. H_2O/L./sec. up to 1.5 L./sec. both with an increase in end-expiratory level and with the FRC restored to that present in the unloaded state. Eight healthy male individuals aged 21-34 years (five non-smokers and two smokers) with no evidence of pulmonary disease were studied.

All studies were carried out while the subjects sat in a body box and breathed in and out of a 9 liter Collins spirometer which was situated outside of the box. Continuous recording of the tidal volume with the spirometer while in the unloaded state and during resistance loading allowed measurement of the change in end-expiratory level induced by the external resistance.

Two techniques were used to study the ventilatory response to carbon dioxide:-

A) A modification of the rebreathing technique of Read (11, 32).

B) Breathing through varying lengths of added dead space (8).

The ventilatory response to carbon dioxide was measured by each technique in five subjects and by both techniques in two subjects.

End-tidal gas was collected continuously with an end-tidal sampler and measured for carbon dioxide concentration by a Beckman LBI CO_2 analyzer. After being recorded, the sample was returned to the spirometer.

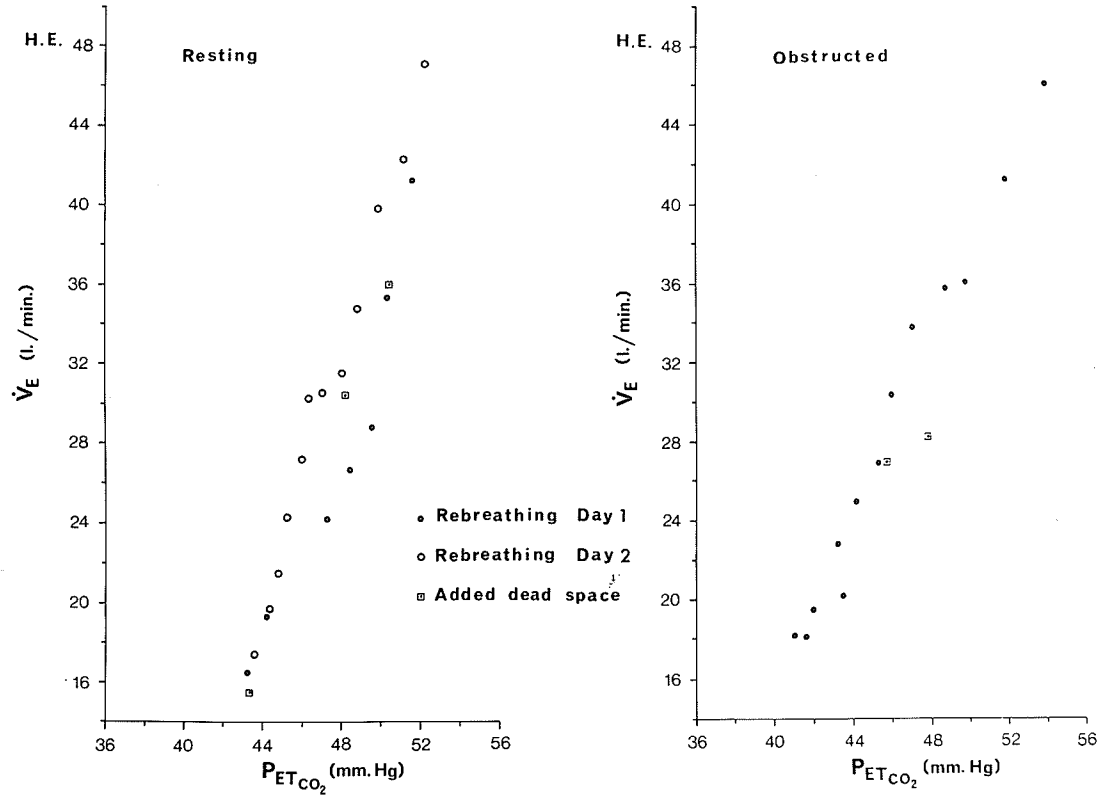
During measurements utilizing the rebreathing technique of Read, the mean end-tidal carbon dioxide concentration and minute ventilation over 24 second periods were determined and the relationship between $P_{ET_{CO_2}}$ and $\dot{V}_E$ determined.

In the second series of studies, the ventilatory response to carbon dioxide was determined by measurement of the ventilation and end-tidal pCO_2 induced by the addition of various lengths of dead space. Measurements of ventilation, end-tidal carbon dioxide concentration and change in the end-tidal level induced by the external resistance were monitored continuously for a minimum of eight

minutes and all measurements were made over a three minute period after the end-tidal carbon dioxide and end-expiratory level were stable. Restoration of the end-expiratory level to that present in the unloaded state was achieved by applying a positive pressure around the body in the body box.

The reproducibility of the rebreathing technique on two separate occasions without added external resistance as well as a comparison of measurements obtained with the two techniques with and without external resistance is demonstrated in Figure 1.

Fig. 1


H.E.
Resting
$\dot{V}_E$ (l./min.)
$P_{ET_{CO_2}}$ (mm. Hg)
Rebreathing Day 1
Rebreathing Day 2
Added dead space
H.E.
Obstructed
$\dot{V}_E$ (l./min.)
$P_{ET_{CO_2}}$ (mm. Hg)

C. RESULTS

The effect of added resistance with and without an increase in end-expiratory level on the ventilatory response to carbon dioxide in five subjects utilizing the rebreathing technique is presented in Figure 2.

The ventilatory response to carbon dioxide was reduced by the addition of the external resistance in all of the subjects. It can be seen that in three of these subjects there was an increase in ventilatory response to carbon dioxide when the body box was pressurized in an attempt to return the end-expiratory level to that present in the unloaded state. In two of the subjects who demonstrated a reduction in response with added resistance, there was no change following the addition of positive pressure in the box.

Since it was not possible to ensure that the end-expiratory level during resistive loading had been restored to that present in the unloaded state technique, a second series of studies utilizing the added dead space, and which allowed continuous monitoring of the end -expiratory level, were carried out.

Figure 3 presents the effect of resistive loading with and without an increase in end-expiratory level on the ventilatory response to carbon dioxide using the dead-space technique in five subjects. Twelve measurements of carbon dioxide response during added resistance with and without added pressure were carried out. For each subject a mean line is drawn through measurements of $P_{ET}CO_2$ and $\dot{V}_E$ obtained while breathing at rest without added resistance. It can be seen that the points representing the relationship between $P_{ET}CO_2$ and $\dot{V}_E$ while breathing through added resistance fall below those observed in the unloaded state. When the end-expiratory level was restored to that present in the unloaded state by the institution of a positive pressure in the body box, there was a significant increase in $\dot{V}_E/P_{ET}CO_2$ relationship, the values obtained acutally exceeding those in the unloaded state.

This is further demonstrated in Figure 4, in which minute ventilation with added resistance is compared to that calculated at an equivalent $P_{ET}CO_2$ in the unloaded state. It can be seen that the ventilation was reduced to a varying extent from the unloaded state by the addition of a non-elastic resistance. Following restoration

Fig. 2

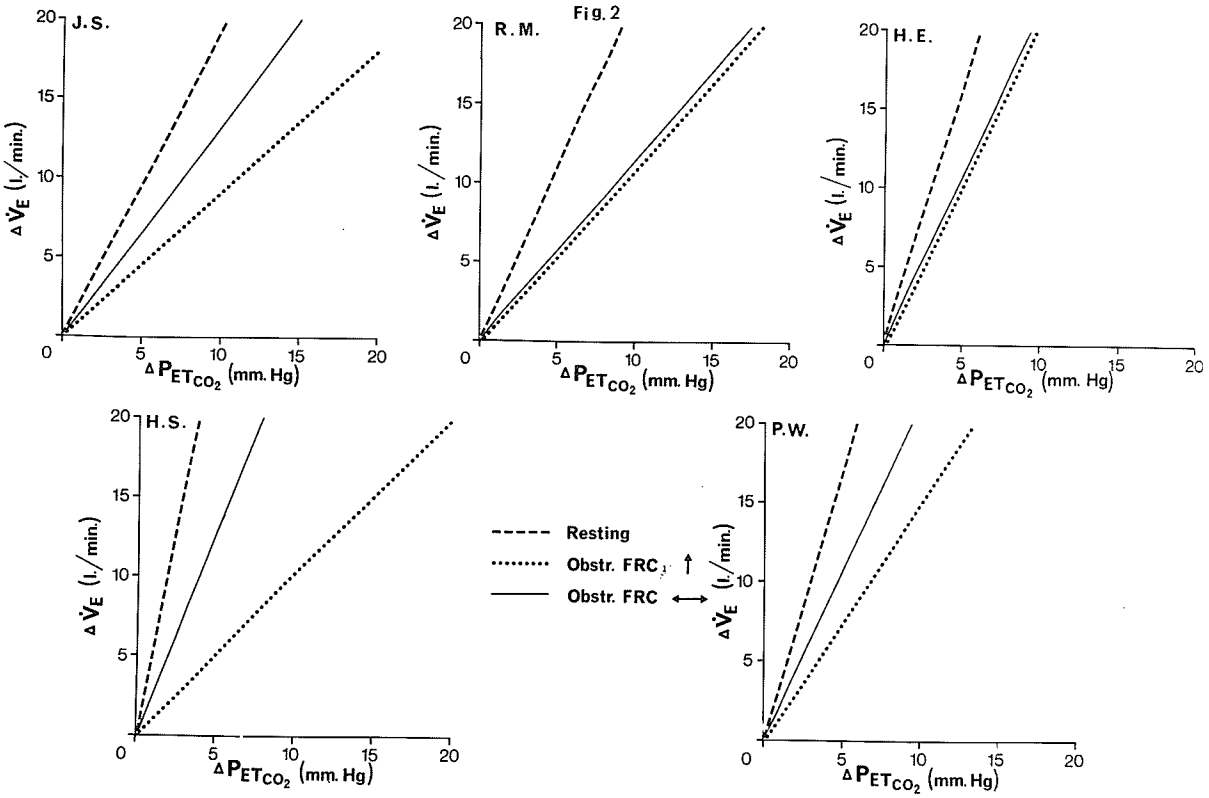

J.S.
R.M.
H.E.
H.S.
P.W.
$\Delta \dot{V}_E$ (l./min.)
$\Delta P_{ET_{CO_2}}$ (mm. Hg)
0
5
10
15
20
Resting
Obstr. FRC ↑
Obstr. FRC ↔

Fig. 3

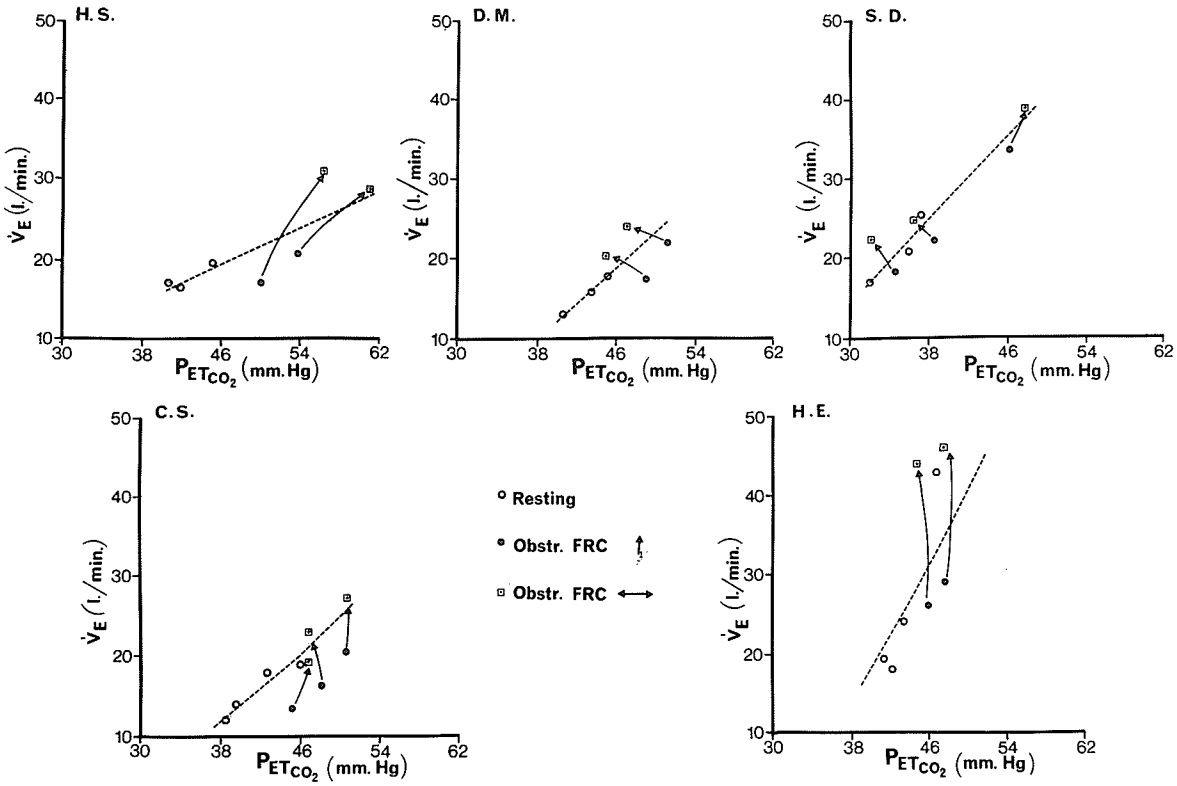

H. S.
D. M.
S. D.
C. S.
H. E.
$\dot{V}_E$ (l./min.)
$P_{ET_{CO_2}}$ (mm. Hg)
50
40
30
20
10
30
38
46
54
62
Resting
Obstr. FRC
Obstr. FRC

Fig. 4

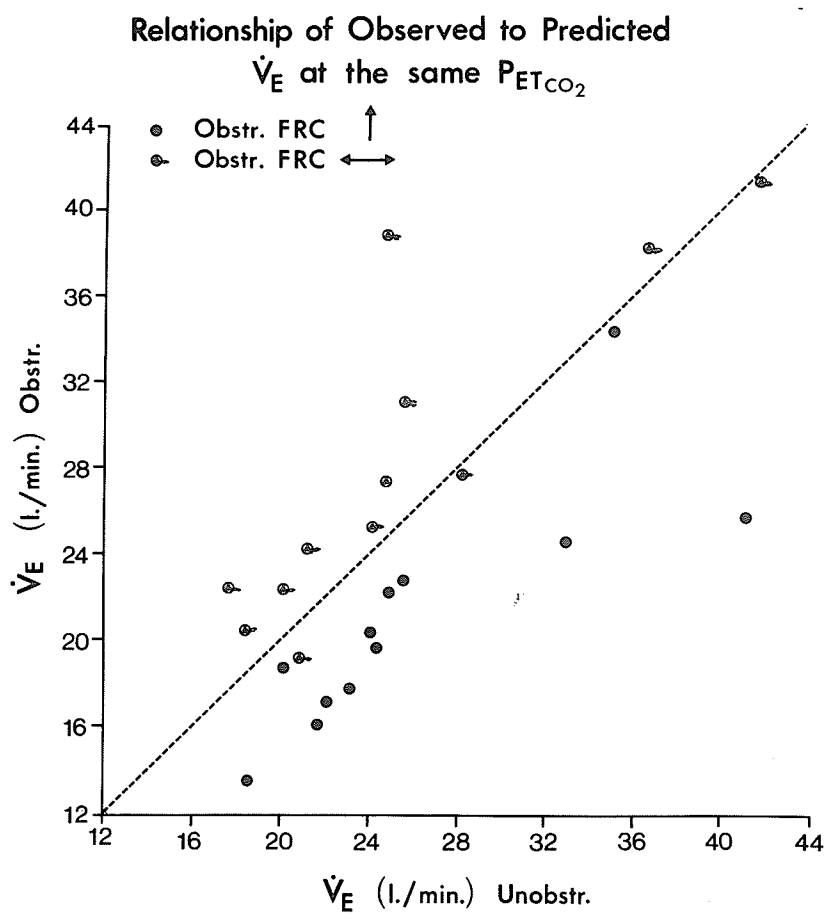
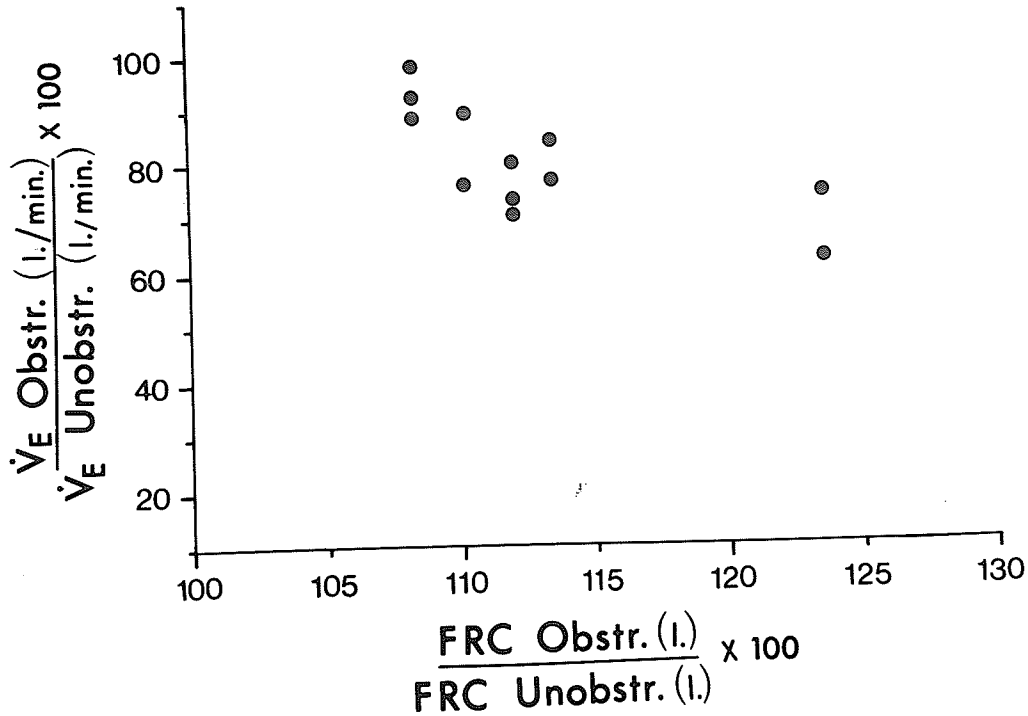

Relationship of Observed to Predicted
$\dot{V}_E$ at the same $P_{ET_{CO_2}}$
Obstr. FRC
Obstr. FRC
$\dot{V}_E$ (l./min.) Obstr.
$\dot{V}_E$ (l./min.) Unobstr.
12
16
20
24
28
32
36
40
44

Fig. 5


$\frac{\dot{V}_E \text{ Obstr. (l./min.)}}{\dot{V}_E \text{ Unobstr. (l./min.)}} \times 100$
100
80
60
40
20
100
105
110
115
120
125
130
$\frac{\text{FRC Obstr. (l.)}}{\text{FRC Unobstr. (l.)}} \times 100$

of the end-expiratory level to that present during the unloaded state, the ventilation at a particular pCO_2 was increased significantly and was greater than that seen in the unloaded state in nine of the twelve studies.

Figure 5 presents the relationship between the change in FRC and the change in $\dot{V}_E$ at an equivalent pCO_2 following the addition of the external resistance. Absolute FRC during obstruction was calculated by addition of the FRC measured while at rest and the increase in FRC during loading. It can be seen that the fall in ventilation induced by external resistance appeared to be related to the proportional age increase in end-expiratory level ($r = 0.738$, $p < .01$).

D. DISCUSSION

The reduction in ventilatory response to carbon dioxide in normal subjects by non-elastic loading agrees with previous reports (5, 7, 9, 15, 21, 22, 26). However, the mechanism by which external resistance loading diminished the ventilatory response to carbon dioxide has not been clearly elucidated. The data presented in this paper suggest that an increase in end-expiratory level may play a major role, and there are several possible mechanisms by which this may take place. The reduction in ventilatory response to carbon dioxide may be due to:-

a) an alteration of the internal resistances because of the increase in end-expiratory level, i.e. the individual is now breathing at a level on the flatter portion of the pressure/volume curve.

b) a reduced mechanical efficiency of the respiratory system at high lung volumes so that although the respiratory center responds normally to the carbon dioxide stimulus, the ventilatory output is reduced.

c) an alteration of lung reflexes which stimulate or depress the respiratory center at different lung volumes.

d) an acute change in the sensitivity of the chemosensitive areas in the CNS to carbon dioxide.

A. Alteration of Internal Resistances

An upward displacement along the pressure-volume curve of the lungs and thorax results in a diminuation in airway resistance and a rise in elastic resistance of the respiratory system. If the latter were to predominate, it is possible that the increased internal elastic load could result in a reduced ventilatory response to carbon dioxide. The application of pressure around the body, although restoring the end-expiratory level to the normal resting position and thereby possibly reducing the internal elastic load would however impose an additional external elastic load. Thus the ventilatory response to carbon dioxide should theoretically decrease when the FRC was restored rather than increase. Thus it is unlikely that additional elastic loading can account for the reduction in response to carbon dioxide.

B. Reduced Mechanical Efficiency of the Respiratory Muscles

The maximum pressure generated in the respiratory system by the respiratory muscles is dependent on the lung volume (3, 12, 25, 26, 31). Flenley et al have shown that the tidal volume response to inhaled carbon dioxide during positive pressure breathing varies with the degree of pressure applied, and have attributed the fall in response to a mechanical impairment of the inspiratory muscle action at high lung volumes (17). Similarly it is possible that an alteration in the mechanical efficiency of the respiratory muscles associated with an increased end-expiratory level played a significant role in the reduced ventilatory response to carbon dioxide observed in the subjects with external resistance loading.

C. Pulmonary Reflexes

It has been shown that stimuli arising from stretch receptors in the lungs cause depression of centrally mediated inspirations, and that the vagal discharge for this reflex is dependent on lung volume (1, 23). Thus reduction in diaphragmatic activity in response to carbon dioxide with increasing lung volume has been demonstrated by Woldring (40) and Stanley et al (38) in animals. In addition, Mithoefer et al (28) in humans suggested that this Hering-Breuer reflex was operative in depressing breath holding time, the maximum depression occurring at complete lung inflation and the maximum stimulation occurring at full expiration.

A positive interaction of neural reflexes with carbon dioxide responsiveness has also been demonstrated in human subjects by Guz et al (19) who found a reduction in ventilatory response to carbon dioxide after local anaesthetic block of the vagus and glossopharyngeal nerves in the neck.

D. Acute Changes in the Sensitivity of the Respiratory Center

A change in the sensitivity of the respiratory centers to carbon dioxide because of an increased buffering capacity by bicarbonate has been implicated in the reduced ventilatory response to carbon dioxide in patients with emphysema (2, 14, 30, 36, 37), and healthy subjects after chronic exposure to carbon dioxide (35). While an acute change in central sensitivity to carbon dioxide may have occurred with resistance loading, it is unlikely to have been revised with restoration of the end-expiratory level.

It is possible that the increase in ventilatory response to carbon dioxide when positive pressure surrounded the body was due to an added respiratory stimulus, and was not related to the restoration of the end-expiratory level to that present in the unloaded state.

Thus in animal experiments it has been shown that if the vagi are intact, stimulation of respiration occurs when expansion of the chest is restricted by external chest pressure (4, 18, 20) or negative pressure breathing (13). The increase in minute ventilation was due to a significant increase in respiratory rate, the tidal volume remaining unchanged. Whatever the explanation for the effect of lung volume on the ventilatory response to carbon dioxide, it would appear that the increase in lung volume resulting from external resistance loading may be a major factor in limiting the ventilatory response to inhaled carbon dioxide when the resistance to air flow is increased. It is possible that this may also explain the reduced ventilatory response to carbon dioxide seen in patients. Thus, Tyler and Grape (39) showed an improvement in the ventilatory response to carbon dioxide when using a servo-controlled patient cycled respirator.

It may also explain the difference between elastic and non-elastic loading on ventilatory response to carbon dioxide. It has been shown that the end-expiratory level increases with non-elastic loading (26) but not with elastic loading (26). Finally, it may also account for the fact that patients demonstrate a normal ventilatory response to carbon dioxide with pulmonary fibrosis or other restrictive lung disorders.

E. SUMMARY

The effects of returning the end expiratory level to normal on the ventilatory response to carbon dioxide when breathing with an increased non-elastic resistance was studied in eight subjects using two techniques.

With the rebreathing technique in which the end expiratory level could not be continuously monitored, pressurization of the box to a predetermined positive pressure resulted in improvement of the ventilatory response to carbon dioxide in three of the five subjects studied. With the added dead space technique in which the end expiratory level was continuously monitored, restoration of the end expiratory level to normal produced a significant increase in the minute ventilation in the five subjects studied. This improvement was the result of an increase in respiratory rate without any significant change in the tidal volume. A direct relationship was seen between the fall in observed minute ventilation and the increase in F.R.C. following the addition of the external non-elastic resistance.

These findings demonstrate that the position of the end expiratory level is important in determining the ventilatory response to carbon dioxide. The mechanism by which the position of the end expiratory level produces this change has not yet been resolved.

F. ACKNOWLEDGMENTS

The author wishes to thank Dr. Reuben M. Cherniack for the stimulation, advice and critical evaluation which he provided during the course of this study. The assistance of Dr. Arnold Naimark in the planning of this program is gratefully acknowledged. The technical assistance of Mr. Suresh Dhingra was invaluable during this study.

This work was supported in part by the Medical Research Council of Canada Grants held by Dr. Reuben M. Cherniack and Dr. Arnold Naimark and in part by a Mead-Johnson Residency Scholarship of the American College of Physicians held by the author.

G. BIBLIOGRAPHY

1. Adrian, E.D.: Afferent impulses in the vagus and their effect on respiration. J. Physiol. 79:332-358, 1933.

2. Alexander, J.K. J.R. West, J.A. Wood, and D.W. Richards: Analysis of the respiratory response to carbon dioxide inhalation in varying clinical states of hypercapnia, anoxia and acid-base derangement. J. Clin. Invest 34: 511, 1955.

3. Agostoni, E. and J. Mead: Statics of the respiratory system Handbook of Physiol. Sec 3, 1: 387-409 Washington D.C. Amer. Physiol Soc., 1964.

4. Bakos, A.C.P. and W.L. Howell: Constriction of the mid-Thorax as a means of reflex maintenance of respiration during barbiturate narcosis, Science. 108: 45-46, 1948.

5. Barnett, T.B. and B. Rasmussen: Ventilatory Responses to hypoxia and hypercapnia with external airway resistance. Act. Physiol. Scand. 80: 538-551, 1970.

6. Brodovsky, D., J. A. MacDonnell, and R.M. Cherniack: The Respiratory response to carbon dioxide in health and emphysema. J. Clin. Invest. 39: 724-729, 1960.

7. Cain, C.C. and A.B. Otis: Some physiological effects effects resulting from added resistance to respiration. J. Aviation Med. 20: 303-308, 1957.

8. Cherniack, R.M.: The oxygen consumption and efficiency of the respiratory muscles in Health and Emphysema. J. Clin. Invest.: 38, 494-499, 1959.

9. Cherniack, R.M. and H. Levison: Influence of mechanical resistances on ventilatory response to hypercapnia and hypoxia; In press, 1972.

10. Cherniack, R.M. and D.P. Snidal: The effect of obstruction to breathing on the ventilatory response to CO_2. J. Appl. Physiol. 14: 721-726, 1959.

11. Clark, T.J.H., B.G. Clarke, and J.M.B.Hughes: A simple technique for measuring changes in ventilatory response to carbon dioxide. The Lancet, 2: 368-371, 1966.

12. Cook, C.D., J.Mead, M.M. Orzalesi: Static volume pressure characteristics of the respiratory system during maximum efforts. J. Appl. Physiol. 19: 1016-1022, 1964.

13. Culver, G.A., and H. Rahn: Reflex respiratory stimulation by chest compression in dogs. Am. J. Physiol. 168: 686-693, 1952.

14. Donald, K.W. and R.V. Christie: The respiratory response to carbon dioxide and anoxia in emphysema. Clin. Sci. 8: 33-44, 1949.

15. Eldridge, R. and J.M. Davis: Effect of mechanical factors on respiratory work and ventilatory responses to CO_2. J. Appl. Physiol. 14: 721-726, 1959.

16. Evan, E.L., and A.V. Hill: Relation of length to tension developed and heat production on contraction in muscle. J. Physiol. (Lond.) 49: 10, 1914.

17. Flenley, D.C., L.D. Pengelly, and J. Milic-Emili: Immediate effects of positive pressure breathing on the ventilatory response to CO_2. J. Appl. Physiol. 30: 1, 7-11, 1971.

18. Gessell, R., and C. Moyer: Proprioceptive reflex effects arising from deformations in the lungs and torso. Am. J. Physiol. 133: 293, 1941.

19. Guz, A., M.I.M. Noble, J.G. Widdicombe, D. Trenchard, W.W. Mukin and A.R. Makay: The role of vagal and glosso-pharyngeal afferent nerves in respiratory sensation, control of breathing and arterial pressure regulation in conscious man. Clin. Sci. 30: 161-170, 1966.

20. Hammouda, M. and W.H. Wilson: Vagus influence giving rise to phenomena accompanying expansion and collapse of lungs. J. Appl. Physiol. 74: 81, 1932.

21. Howell, J.B.L.: Breathlessness in pulmonary disease. In Breathlessness. Blackwell Scientific, Oxford, 165-177, 1966.

22. Kellogg, R.H., D.E. Leith, and K. Konno: Ventilatory response to CO_2 when respiratory resistance and elastance are reduced in normal subjects. Fed. Proc. 23: 259, 1964

23. Larrabee, M.G., and G.C. Knowlton: Excitation and inhibition of phrenic motorneurons by inflation of the lungs. Am. J. Physiol. 147: 90-99, 1946.

24. Laurenco, R.V., and J.M. Miranda: Drive and performance of the ventilatory apparatus in chronic obstructive lung disease. New. Eng. J. Med. 279: 53-59, 1968.

25. Marshall, R.: Relationships between stimulus and work of breathing at different lung volumes. J. Appl. Physiol. 17: 917-921, 1962.

26. McIlroy, M.D., F.L. Eldridge, J.P. Thomas, and R.V. Christie: The effects of added elastic and non-elastic resistances on the pattern of breathing in normal subjects. Clin. Sci. 15: 2, 337-344, 1956.

27. Milic-Emili, J., and J.M. Tyler: Relationship between $P_{A_{CO_2}}$ and respiratory work during external resistance breathing in man. Ann. N.Y. Acad. Sci. 109: 908-914, 1963.

28. Mithoefer, J.C., C.D. Stevens, H.W. Ryder, and J. McGuire: Lung volume, restriction, hypoxia, and hypercapnia as interrelated respiratory stimuli in normal man. J. Appl. Physiol. 5: 797-801, 1953.

29. Pengelly, L.D., M. Kangalee, B. Vadelaga, A. Tarshis, and E.J.M. Campbell: Effects of voluntary control of tidal volumes on the ventilatory response to CO_2 in man. Fed. Proc. 31: 2, 810, 1972.

30. Prime, F.J., and E.K. Westlake: The respiratory response to CO_2 in emphysema. Clin. Sci. 13: 321-332, 1954.

31. Rahn, H., A.B. Otis, L.E. Chadwick, and W.O. Fenn: The pressure volume diagram of the thorax and lung. Amer. J. Physiol. 146: 161-178, 1946.

32. Read, D.J.C.: A clinical method for assessing the ventilatory response to CO_2. Australasian Annals of Medicine. 16: 20, 1966.

33. Richardson, P.S., and J.G. Widdicombe: The role of the vagus nerves in the ventilatory responses to hypercapnia and hypoxia in anaesthetized and unanaesthetized ribbits. Resp. Physiol. 7: 122-135, 1969.

34. Riley, R.L.: The work of breathing and its relation to respiratory acidosis. Ann. Int. Med. 41: 172-176, 1954.

35. Schafer, K.E.: Atmung und saure-basengleichgewicht bei langdauernden aufenthalt in 3% CO_2. Pfluger's Arch. ges Physiol. 251: 689, 1949.

36. Scott, F.H.: On the relative parts played by nervous and chemical factors in the regulation of respiration. J. Physiol. (Lond.) 301-326, 1908.

37. Scott, R.W.: Observations on pathologic physiology of chronic pulmonary emphysema. Arch. Int. Med. 26: 544-560, 1920.

38. Stanley, N.N., P.G. Tuleur, M.D. Altose, and N.S. Cherniack: Interaction of lung volume and chemical stimuli on respiratory drive. Fed. Proc. 31: 815, 1972.

39. Tyler, J.M., and B. Grape: The influence of mechanical assistance to respiration on the ventilatory response to carbon dioxide in emphysema. Amer. Rev. Resp. Dos. 86: 29-36, 1962.

40. Widdicombe, J.G.: Respiratory reflexes. Handbook of Physiol. Washington D.C., Amer. Phys. Soc., 1964, Sec. 3, pp. 585-630.

41. Woldring, S.: Interrelationship between lung volume, arterial CO_2 tension and respiratory activity. J. Appl. Physiol. 20: 647-652, 1965.

42. Wood, W.B., and T.B. Barnett: Effects of Helium mixtures on ventilatory response to CO_2 in subjects with airway obstruction. Clin. Res. 8: 77, 1965.