PRESSURE-LUNG VOLUME RELATIONSHIP AND ELECTROMYOGRAPHY OF INSPIRATORY MUSCLES IN MAN DURING PARTIAL CURARIZATION

by

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ABSTRACT

Saunders and his associates reported that during submaximal neuromuscular blockade, vital capacity was reduced to a greater extent than would have been predicted according to the reduction in the maximal inspiratory pressure in a simple mechanical model (J. Appl. Physiol. 44:589,1978). Disproportionate respiratory muscle weakness and a different recruitment pattern for different voluntary efforts were proposed as possible explanations.

This issue was addressed by measuring the rectified electromyogram of the diaphragm, intercostal, scalenes, and sternomastoid muscles during maximal and submaximal static inspiratory manoeuvres. Two studies were performed. The control series of experiments showed that at very low levels of static pressure, only the diaphragm was activated. Further increases in pressure then recruited the intercostal/accessory muscles, in some subjects more than in others. There was generally an orderly increase in the rectified EMG in all muscles with elevations in pressure. For particular levels of pressure to be produced at lung volumes above the relaxed end-expiratory position, the EMG was increased. Compared to the maximum EMG elicited with

maximal static pressures or full inspirations, resting ventilatory requirements still leave a large myo-electric reserve.

In the submaximal neuromuscular block study, the mean maximal inspiratory pressure was decreased from 103 to 39 cm H20, but only two of the five subjects behaved in the manner observed by Saunders and his associates. There was no clear evidence that the diaphragm was less affected than the other muscles. In many cases however, a submaximal level of pressure was achieved by augmented EMG in all muscles. It is suggested that curare interferes with the conversion of electrical events into whole muscle tension and/or that the impaired chest wall volume compartments are inefficient at producing static pressure.

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INTRODUCTION

I. INTRODUCTION

In healthy individuals, the functional capacity of the respiratory musculature appears to be in excess of most physiological requirements. Even during high-intensity exercise, muscle pressure and air flow rarely approach their maximum [180], and alveolar ventilation is sufficient to maintain the arterial blood gas tensions [77]. In the presence of nerve and/or muscle disorders however, respiratory muscle pressure can become inadequate and respiratory failure result if assisted ventilation is not provided.

Pharmacologically-induced conditions of acute neuromuscular weakness can mimic the clinical picture. Not only do they further our understanding of the manner in which the respiratory system copes with weakened or fatigued muscles, but insight is offered into other fundamental properties of skeletal muscle.

The investigations reported in this thesis were stimulated by the observation that during submaximal neuromuscular blockade, vital capacity was reduced to a greater extent than would have been predicted according to the reduction in the maximal inspiratory pressure in a simple

mechanical model [232]. Disproportionate respiratory muscle weakness and a different recruitment pattern for different voluntary efforts were proposed as possible explanations.

This issue was addressed by measuring the rectified electromyogram of the diaphragm, intercostal, scalenes, and sternomastoid muscles at the time of maximal and submaximal static inspiratory manoeuvres before and during partial curarization. This would determine the level of activation, relative to that at maximal inspiration, over the full range of respiratory pressures for the four muscles. If curare affects particular muscles more than others, the manoeuvres in which their recruitment was extensive originally, would be expected to be most impaired. Specifically, it was hypothesized that if the inspiratory capacity was more impaired than the static inspiratory pressure, then the extra-diaphragmatic muscles would show greater reductions in their electromyograms than the diaphragm.

CHAPTER II

REVIEW OF LITERATURE

II.A. RESPIRATORY MUSCLES

II.A.1. Action of the Respiratory Muscles

For air to enter the lungs, a pressure differential must occur between the environment and the alveoli. This differential is developed by the inspiratory respiratory muscles which expand the thorax causing a decrease in the intrapleural pressure. The pressure difference across the lungs enlarges the alveoli to produce a momentary decrease in the alveolar air pressure. Since alveolar pressure is now less than atmospheric pressure, air flows into the lungs following the gradient. Pressure equalization is finally reached at the end of the breath when inspiratory muscle contraction ceases. Expiration is usually the reverse process where primarily elastic forces increase alveolar pressure above atmospheric and air flows out. Unless specifically stated otherwise, the focus of all discussion in this thesis is on inspiratory events.

A full description of the mechanical events during the breathing cycle would consider the muscles undergoing contraction, the forces which result from such contraction,

and any motion of parts produced by those forces [45]. Rarely can this be accomplished because it is difficult to determine whether movement of any particular part of the respiratory system is the cause or the effect of muscular forces. In addition, consideration must be given to those parts which do not move. Whether it is a rigid structure or a muscle contracting isometrically, the participation may be critical to the smooth performance of the inspiratory act.

Our early understanding of the muscular aspects of breathing is due to the immense contribution of Duchenne [82]. From extensive clinical studies and the use of Faradic stimulation on man, recent cadavers, and animals, he observed that diaphragmatic contraction caused the ribs to move in an upward and outward direction. Both the antero-posterior and the lateral diameters of the thorax expanded, the latter much more so. On stimulation of one phrenic nerve, motion was restricted to the ipsilateral side. Inward airflow could be heard in these experiments, even in dead animals. He recognized the importance of an abdominal fulcrum when the contracting diaphragm pulled in the lower rib cage in studies with evisceration. To illustrate the force of the diaphragm, he described that applying the fist to the inferior aspect of the central tendon in horse only minimally prevented the diaphragm's movement downward.

Using radiological techniques, Wade [260] was one of the first to quantitate the movement of the diaphragm.

During quiet breathing in the upright posture, he observed that the diaphragm descended by a mean value of 1.65 cm. The inspired volume, as monitored by the spirogram, was 799 ml. When a deep inspiration of 3200 ml was made, the thoracic cage was lifted vertically by 2.6 cm while the diaphragm's excursion relative to the ribs was approximately 10.3 cm, ranging from 7 to 13 cm. The chest circumference increase varied from 5 to 11 cm. When the supine posture was assumed, the amount of diaphragm movement did not change but the position at the beginning of the breath was more cephalad. Wade's calculations of the diaphragmatic contribution to a large inspired volume, approximately three-fourths of the total volume, has often been quoted. However, his simultaneous equations were solved using diaphragm and thoracic cage displacements which were obtained in different postures. The calculations would be reasonable estimates only if the relative contributions of the two parts is constant in the two positions.

With electromyography it is possible to demonstrate specific muscle involvement. Action potentials are produced only when muscle fibres are stimulated to contract. Campbell [44] was the first to use this technique extensively on respiratory muscles but he realized that although the electromyogram (EMG) illustrated the circumstances in which muscle contracted, it alone did not provide information on the muscle's mechanical action or its specific respiratory

function. (Some predictions of function can be made based on the known origin and insertion of a muscle.) However, when the change in EMG correlates with the intensity of the effort, it strongly suggests a contribution. "Non-specific activity" is likely where no such gradation in EMG is present. This is often seen during maximal muscular efforts. In most subjects, Campbell detected activity in the intercostal muscles during quiet breathing. In the upper intercostal spaces, the activity was less than in the lower spaces. It could not be determined whether there was actually less contraction or if this was the site of smaller motor units. The scalenes contracted measurably in only some subjects at rest but when the tidal volume reached 40 - 60 % of the inspiratory capacity (IC), all individuals produced EMG in this muscle. The sternomastoids were usually quiet during normal breathing but seemed to be recruited when 70 - 85 % of IC was reached. Of the dynamic thoracic movements, only near-maximum inspirations elicited abdominal muscle contraction. This effect however, was also easily produced by slight non-respiratory actions of the trunk such as changing posture. When the airway was occluded, abdominal activity was detected with inspiratory efforts of approximately 40 cm H2O and greater.

Following up Campbell's work, Taylor [253] investigated the particular circumstances of contraction of the intercostal muscles with concentric needle electrodes. This

technique has the advantage over surface electrodes in that the EMG is uncontaminated by overlying, non-respiratory skeletal muscle such as the pectoralis. In most parts of the thoracic cage, two layers of intercostal muscle could be determined. Inspiratory behaviour was confined to the external layer while the internal layer was active during expiration. The parasternal region however, appeared to behave differently. Anatomically, these muscles are part of the internal intercostals but they contracted only during inspiration. They were even active during quiet breathing. In some subjects, this pattern extended down to the fifth intercostal space. Taylor could not confirm Campbell's observation of inspiratory activity in the lower intercostal spaces and suggested that the diaphragm's vertical fibres lying directly beneath such spaces, could have contaminated the earlier results.

Using needle electrodes, Raper and co-workers [219] confirmed the lung volumes at which scalene and sternomastoid electrical activity started.

Several investigations have also considered the possible involvement of other skeletal muscles such as those in the lower thoracic and lumbar region of the back, the trapezius, and the pectoralis. These have been classified as accessory respiratory muscles demonstrating limited involvement in inspiration, and thought to assist in stabilizing the trunk in severe expiratory efforts [44,60,203].

One of the earliest descriptions of direct EMG recording from the human diaphragm was made by Nieporent [203]. He inserted a needle electrode through the intercostal space into the diaphragm at a point just below the phrenic sinus in the right anterior axillary line. Strong electrical activity was observed during inspiration. When a "dyspneic" air mixture of 6% carbon dioxide, 10% oxygen, and 84% nitrogen was breathed, the inspiratory EMG became very strong.

By recording esophageal pressure, abdominal pressure, and the diaphragm EMG with an esophageal electrode, Agostoni and associates [3] and Petit and co-workers [213] were able to relate the behaviour of the diaphragm to particular mechanical events during breathing. As the diaphragm contracted, inspiratory flow began. More importantly, transdiaphragmatic pressure (Pdi), the difference between abdominal pressure and esophageal pressure, was always in phase with flow. The lung can only expand to the extent that pleural pressure becomes more negative and any pressure on the viscera will be noted as an increase in abdominal pressure. Therefore any diaphragm contraction must change Pdi and it has now become accepted as a useful expression of diaphragm force.

When the diaphragm contracts, one of two resulting actions or their combination are possible. This is evident when its anatomical location is considered. Dorsally, the

diaphragm inserts on the second and third lumbar vertebrae and on the medial and lateral arcuate ligaments. As it develops to the side, it inserts on the costal edge of the six lower ribs, rising so that its ventral aspect inserts on the xiphoid process [11]. It may be thought of as a dome with muscular walls and a non-muscular cap. Descent of the central portion of the diaphragm presses directly on the abdominal contents. To the extent that the abdomen may be considered a container of water having only the vertical frontal wall which is compliant [84], the abdomen protrudes forward. The potential pleural space is increased causing the lung to be inflated. If the abdomen offers resistance, as may occur when the abdominal muscles are contracted, the diaphragm cannot descend to any great extent. Since in the relaxed end-expiratory position (e.e.p.) its costal fibres run vertically along the inner wall of the rib cage, on contraction the diaphragm lifts the rib-cage while pushing the lower ribs outward. The movement resembles that of a "bucket-handle". These two possible motions have been described as "abdominal" and "costal" breathing respectively. However as analyzed here and as Wade [260] showed radiologically, diaphragmatic contraction is fundamental to both.

The action of the diaphragm is now believed to be the result of "two muscles". Using direct muscle and phrenic stimulation techniques in dogs, DeTroyer and his

associates [71] separated the behaviour of the costal part of the diaphragm from its crural component. Both parts, when stimulated, increased lung volume, abdominal pressure, and transverse abdominal diameter. The costal part also expanded the lower rib cage while crural stimulation alone had no influence on it. Abdominal pressure had a major effect on the rib cage because with the abdomen open, rib cage expansion by the costal part was only slight and crural stimulation caused paradoxical displacement of the rib cage. The phrenic nerve roots, C5, C6, and C7, were found to innervate, respectively, primarily the anterior costal, the posterior costal and some crural, and primarily the crural parts.

The precise role of the intercostal/accessory muscles is still a source of debate [47]. Taylor's work [253] demonstrated their activity to be simultaneous with inspiration, and Koepke and co-workers [151], also using needle electrodes, found that as the breath became larger, there was progressive recruitment of intercostal muscles beginning with the upper muscles and then spreading to the lower ones. Goldman and Mead [111], and Grimby and associates [120] suggested that, at rest at least, "the diaphragm was the only importantly active muscle". The rib cage appeared to behave as a passive elastic element.

If this indeed is the case, the rib cage should be drawn inward on inspiration due to the increased negativity

of pleural pressure. Such paradoxical motion occurs in quadriplegics whose intercostal muscles are paralyzed. Danon and associates [59] studied respiratory muscle function in quadriplegics with spinal cord lesions at the first cervical vertebra. During spontaneous breathing with the sternomastoids and trapezius, the upper rib cage was expanded but the diameter across the abdomen was reduced suggesting cephalad drawing of the flaccid diaphragm. On mechanical ventilation, both the rib cage and the abdomen were expanded. This procedure shows the true passive elastic behaviour of these parts independent of diaphragm involvement. When phrenic pacing was introduced, the motion of the rib cage was inward, opposite to that seen during mechanical ventilation. These results suggest that in healthy subjects, the diaphragm would drive the rib cage, but in order to prevent distortion and wasted effort, the intercostal/accessory muscles probably have an important stabilizing role.

II.A.2. Static Respiratory Mechanics

As Petit and his associates [213] demonstrated, the mechanical behaviour of the diaphragm can be quantified, but such an analysis is not possible for the other respiratory muscles. Evaluation is therefore made of their net interaction by measuring several different pressures. Furthermore, by studying the sources of resistance to breathing, it is appreciated why these pressures must be developed.

The basis of our understanding of respiratory mechanics has been well described in the edited works of Fenn and Rahn [95] and Campbell and his associates [46]. In a mechanical system such as a bellows pump, the pressure required of the pump to move air can be described by the equation of motion,

$$P = E(V) + R(\dot{V}) + I(\ddot{V})$$

The first term, E(V), relates to the opposition to air flow presented at an instantaneous position of the bellows pump or the bellows volume, V. This is the static component of the overall pressure required. The latter two terms, $R(\dot{V})$ and $I(\ddot{V})$ are dynamic components which deal with instantaneous velocity or flow, and instantaneous acceleration or

volume acceleration, respectively. During the course of a single pump cycle which draws air into the bellows, the terms are not constant and do not reach their maximum values at the same time. The opposition to acceleration reaches its peak at the moment when the direction of air flow changes, e.g. at the completion of expiration and start of inspiration. With respect to velocity, the resistance will be greatest when the air flow rate is greatest. During breathing, this occurs approximately during the middle of inspiration and expiration. The effect of position is maximal at the end of inspiration where elastic recoil of the respiratory system is increased compared to the end-expiratory position. This may be likened to a spring in the bellows which returns the pump to its original position. The maximum opposing pressure of the first term is approximately 3 and 1000 times greater than the second and third terms respectively.

In the studies reported in this thesis, quantitative electromyographic techniques have been used. These methods preclude the investigation of conditions incorporating dynamic muscle contraction because muscle length change and the rate of the change affect the EMG recorded. The effect of flow resistance and inertia on the muscle pressure developed are therefore eliminated. With the emphasis on isometric or near-isometric contractions, muscle pressure deals only with overcoming elastic resistance. The focus of

the next section will be on the mechanical description of the respiratory system in the static state.

When an individual is at his e.e.p., alveolar pressure is identical to atmospheric pressure. If he inhales to his inspiratory capacity and the airway is then quickly occluded while he consciously relaxes all his muscles, the alveolar pressure becomes positive relative to the atmosphere. A typical value is 40 cm H2O, that is, the passive recoil of the respiratory system has a tendency to collapse at that lung volume with a pressure of 40 cm H2O. If one relaxes in a similar manner while at his residual volume, the respiratory system exerts an outward recoil pressure. The alveolar pressure would be approximately -35 cm H2O. Since these are static conditions, the air pressure is identical at all communicating points in the airways of the lung. Therefore, this airway or alveolar pressure can be measured through a port on the mouth side of an occlusion imposed by a respiratory mouthpiece. Recording of alveolar pressure at various lung volumes over the vital capacity range produces a sigmoid-shaped curve on a graph with pressure and lung volume as the abscissa and ordinate respectively. This curve is called the static passive pressure-volume characteristic of the whole respiratory system, Pst(rs). At low lung volumes, alveolar pressure is negative and air would enter as soon as the occlusion was removed. At the e.e.p., the curve passes through zero pressure.

Positive pressures are seen at all lung volumes above e.e.p. A typical curve is shown in Figure 1 which has been reproduced from Agostoni and Mead [4]. Over the mid-volume range where most breathing occurs, the curve is linear. The slope here is the compliance and expresses the proportional change of volume with respect to pressure. A normal value is approximately 0.1 l/cm H20.

Pst(rs) has 2 components. If the lungs could be removed without disturbing the rest of the thorax, the chest wall would have a pressure-volume relationship as described by Pst(w) in Figure 2. The chest wall includes all the intrathoracic and extrapulmonary structures, the rib cage, the diaphragm, the abdominal contents, and the abdominal wall. Its equilibrium point is at a volume position which is greater than the e.e.p. The lungs have a separate pressure-volume relationship as shown by Pst(l) in Figure 2 [4]. As long as it is not collapsed, it always exerts a positive recoil pressure which would tend to cause expiration. At any lung volume, Pst(rs) is the sum of Pst(w) and Pst(l). These inter-relationships were first clearly described by Rahn and associates [216].

To maintain lung volume at the e.e.p., equivalent to approximately 35% of the vital capacity in Figure 2, no muscular effort is required. The tendency for expiration due to lung recoil is opposed by the tendency for inspiration on the part of the chest wall. Therefore, Pst(rs) is zero at

this point. To hold a breath at 55% of vital capacity with the glottis open would require a net respiratory muscle pressure of 9 cm H2O, the same as Pst(rs) at that volume. There is no elastic recoil from the chest wall. All effort is expended to oppose lung recoil. At even higher lung volumes, the muscles must work against both the chest wall and the lung. Herein, we have quantified the first term in the equation of motion, that opposition due to instantaneous position, E(V). The value of E is equivalent to elastance, or the inverse of compliance (1/C). If lung volume were to be increased from e.e.p. by 1.5 l, the elastic pressure which must be overcome by muscle pressure is:

$P = E(\Delta V) = 1/C(\Delta V) = [1/(0.1\ 1/cm\ H2O)] \times 1.5\ l = 15$ cm H2O.

To put a pressure of 15 cm H2O into perspective, we compare it with the maximal pressures the muscles are able to produce [4,54,216]. The results of Figure 3 [4] are achieved by a series of maximal inspiratory and expiratory efforts against an occluded airway. At different lung volumes, the alveolar pressure was measured. The solid lines at the right and left sides of the figure, are the actual pressures measured with the transducer. A maximal inspiratory effort at 80% of vital capacity gives an alveolar pressure of -50 cm H2O. The broken lines are the calculated values for muscle pressure (Pmus). At e.e.p., all the

Pmus is measureable because there is no net elastic recoil to overcome. At 80% vital capacity, maximal Pmus is approximately -75 cm H2O. Of that amount, approximately -25 cm H2O was first necessary to overcome elastic recoil, i.e. Pst(rs) = 25 cm H2O, so that the appropriate lung volume could be reached. Alveolar pressure is still the same as atmospheric pressure. Then the remaining -50 cm H2O Pmus was used to decrease alveolar pressure further. At 100% vital capacity, no inspiratory alveolar pressure can be produced as all Pmus is required to overcome elastic recoil. If alveolar pressure could be reduced further, then there would be extra Pmus available to increase lung volume.

Therefore when a breath of 1.5 l is inspired, the 15 cm H2O of elastic recoil requires only approximately 15% of the maximal Pmus at that elevated lung volume. The reserve of Pmus however is reduced dramatically when the pressure required for a breath is increased, e.g. with pulmonary fibrosis or restricting garments, or if the Pmus available is reduced as may occur with muscle weakness or hyperinflation.

In preparation for the manner in which some of the results of this investigation will be reported, the usefulness of esophageal pressure is presented. In Figure 2, the pressure-volume curve of the lung shows that at any volume, the lung's tendency to collapse is described by a positive alveolar pressure. It is equally accurate to express this

same recoil as a tendency to pull away from the inside of the chest wall. This pressure is negative in direction but the magnitude is the same. When alveolar pressure becomes negative during a static inspiratory effort, the average pleural pressure changes by the same amount [48]. On an absolute scale however, it will be more negative than the alveolar pressure by an amount due to the recoil of the lung. For example, at 1 l above the e.e.p., alveolar pressure is zero but -Pst(l) is approximately -10 cm H2O. If an inspiratory effort decreases alveolar pressure to -50 cm H2O, the average pleural pressure would be -60 cm H2O. Pleural pressure changes are reliably recorded with an esophageal balloon [186]. Esophageal pressure (Pes) has several advantages. (1) During respiratory manoeuvres with a closed glottis or buccal muscle recruitment, alveolar pressure is not properly indicated by mouth pressure. (2) Esophageal pressure is an instant indicator of respiratory muscle activation. (3) Pmus can be determined as the difference between Pst(w) for the appropriate lung volume and Pes.

II.B. MECHANICS AND ELECTROMYOGRAPHY OF SKELETAL MUSCLE

In this research, the static analysis of respiratory muscle function must be considered within three aspects: the gradation of force, the relationship of force and EMG, and the production of force at different muscle lengths. These features are essential factors in breathing since the inspiratory muscles continuously exert an increasing force while shortening.

The force produced by a muscle's contraction is related to the number of motor units stimulated, the stimulation rate of these motor units, and the number of fibres within the motor unit. Based on isometric contractions in cat muscle experiments, Liddell and Sherrington [163,165] introduced the term "recruitment". When the excitation intensity of repeating submaximal stimuli of a motoneurone was abruptly increased, the myogram recording increased in a manner identical to the tension change observed on the initial start of stimulation. Then in the extensor reflex, tension increased very slowly, often requiring ten to twenty times as long to reach maximal force as was required for flexion reflexes. Assuming that these tension changes could

only be the result of additional contracting muscle units, they speculated recruitment of fresh motor neurons. This was verified when, in similar preparations, the surface compound action potential increased in amplitude with the elevation in tension [55]. When decreasing intensities of stimulation of the inhibitory afferent nerve was performed on reflexively excited knee extension, the extensor myogram showed an increasing resistance to inhibition. Liddell and Sherrington [164] postulated that "motor units", the motor neuron and its muscle fibres, combine in various numbers to cause the graded response in muscle tension [240]. The individual motor unit seemed to behave in an all-or-none manner. Denny-Brown [78] identified that action potentials of different shape and frequency belong to different motor units and also concluded that the intensity of reflex muscle contractions was related to the number of active units.

Several years after the reports of Liddell and Sherrington, Adrian and Bronk [1] divided motor nerve trunks with fine needles so that the electrical activity could be recorded from only several intact nerve fibres. In response to various intensities of pinching the foot of cats, the frequency of discharge of the reflexively stimulated nerve fibres increased with more forceful contractions. Depending on the muscle innervated, initial firing rates of 5 to 10 Hz were observed, but reflexive behaviour could increase the rate to 25 - 40 Hz. Postural reflexes could elicit

frequencies of 90 Hz.

When tension is recorded as a muscle is stimulated at different frequencies, an S-shaped curve is produced. From frequencies approximating 5-10 Hz, large increases in force are achieved with more rapid levels of excitation. As higher firing rates of approximately 20-30 Hz are produced, the tension increases are less dramatic and eventually achieve an asymtote [56]. The motor unit fibre type will determine the particular inflection points in the force-frequency relationship.

During a single excitation of a muscle fibre, the active state of the contractile filaments must first stretch the lightly damped, series elastic component before isometric force or shortening can occur. The rapid addition of a second stimulus prolongs the active state and produces a greater force response because less tension is wasted in extending the already stretched series elastic component. A third rapid stimulus would increase the tension again [41] but by a lesser amount. It is the maximum tension at a given stimulation rate which is depicted in graphs of force and frequency.

To assess the contributions of motor unit recruitment and discharge frequency to the gradation of force, Milner-Brown and his collegues [188,189] correlated the firing of particular single motor unit action potentials with the immediate force produced. Recruitment was the major

mechanism for increasing tension initially, at least in the human first dorsal interosseus muscle. At intermediate and high force levels, increases in firing frequency from 8 Hz to 20-30 Hz predominated and would therefore be the major controller of force over normal activity levels. This pattern was verified by Monster and Chan [194] who recorded single potentials from several hundred motor units during isometric contraction of extensor digitorum communis. New motor units were recruited with small increases in total muscle force, but over a doubling of the initial firing frequency of many units occurred within the large range of force of 10-50 times the initial tension. The excitation rate increased more quickly the longer the delay for a motor unit to participate.

Other evidence however suggests that recruitment is the main determinant of a muscle's force production. In the abductor digiti minimi brevis muscle studied by Bigland and Lippold [24], firing frequency increases from 15 to 25 Hz and 35 to 45 Hz increased muscle tension from rest to 25% MVC and from 75 to 100% MVC respectively. Over the 25 to 75% MVC range, there was a relative frequency plateau from 25 to 35 Hz suggesting that motor unit recruitment must have been responsible for the large increase in force in this intermediate range. Clamann [50] came to the same conclusion when in biceps brachii muscle he only found dramatic changes in firing frequency at the low and high force range.

His overall frequency range however was more narrow than that observed by Bigland and Lippold.

From experiments which have utilized primarily reflex stimulation, the manner in which motor units are recruited appears to follow a "size principle" [126]. Slow firing motor units develop small force, have a long contraction time, and have motor neurons with a small soma and narrow axons. These are activated when low levels of force are produced. In man these units are often associated with tonic activity whereas phasic contractions involve those with higher discharge rates [123]. Small motoneurones are more susceptible to discharge because they exhibit larger excitatory post-synaptic potentials. This is postulated to be related to the total synaptic input current produced on the motoneurone and the resistance of the membrane to this current [127].

Muscle fibre contraction is preceded by the propagation of an action potential along its sarcolemma. When a number of these action potentials are recorded by an electrode nearby, the electromyogram represents the spatial and temporal superposition of those potentials [61]. Of the various technical factors which determine the precise shape of the EMG (see DeLuca [61] for details) the following discussion will deal only with electrical events occurring in muscle. In terms of the total electrical activity, and its relation to muscle tension, EMG recorded with surface

electrodes indicates the same relative changes as those obtained from intramuscular electrodes [33]. This is not the case with fatiguing contractions however [248].

Since the work of Lippold [169], to be described below, attempts to infer muscle force from EMG records have become common. This is logical in light of the previous discussion. Increasing firing frequency, and recruitment both increase the number of muscle fibre contractions/unit of time. Therefore the number of action potentials increases which in turn causes greater amplitudes in the EMG. As will become apparent however such reasoning is an oversimplification.

Lippold [169] measured the mean integrated EMG of three 1/6 sec segments of a 5 sec isometric contraction from the gastrocnemius-soleus group. The EMG increased linearly with force increases although Lippold was not explicit on the upper limit over which this occurred. Other investigators have also reported linear relationships [136,196,245].

In contrast, many have observed relationships in which the EMG changes are greater than the force increases, particularly at high intensity levels [157,184,259,269]. Bigland-Ritchie and Woods [26] discuss this apparent controversy offering several explanations. (1) Some muscles may be limited by their relatively few motor units and depend more on modulation of firing frequency than recruitment. (2) Results from different studies may not be comparable if

the manner in which a given level of force production was changed e.g. ramps of continually changing tension vs. series of isometric contractions, vs. rapid onset of tension, etc. (3) Motor unit recruitment alone could linearly increase the EMG with force increases but the fibres added would have to be of uniform size with similar amplitude action potentials randomly distributed throughout the muscle. In the first dorsal interosseus at least, units recruited later contribute larger amplitudes to the surface EMG [190]. (4) Fatigue causes disproportionately more EMG for a given level of force [86]. (5) Finally, the functional position of a motor unit on its force-firing frequency characteristic must be considered. On the steep portion, increases in the rate of stimulation produce more force while increasing the number of action potentials. If the muscle fibres are near tetanus, little added force can be expected despite further increases in firing rate. Bigland-Ritchie and her associates [27] subsequently reported that linear relationships between the smooth-rectified EMG and force were observed in muscles of predominantly uniform fibre composition (soleus and adductor pollicis) and those which depend mainly on firing frequency for controlling tension (adductor pollicis and first dorsal interosseus). Non-linear relations were obtained from muscles of mixed fibre types which would recruit different types of motor units at different overall contraction

intensities, (biceps, triceps, brachii, brachioradialis) and in a muscle which changes its force primarily through recruitment, the biceps brachii. Milner-Brown and Stein [190] have expressed the following caution - "EMG potentials and contractile responses may both sum non-linearly at moderate to high force levels, but in such a way that the rectified surface EMG is still approximately linearly related to the force produced by the muscle." In the discussion of force and of EMG, no mention was made of muscle length, yet changes in this condition influence the expression of both of these aspects of muscle function.

Since the work of Blix [30], as cited by Ralston and associates [217], it has been realized that the maximum force a muscle can produce during an isometric twitch, or during tetanus, occurs at a muscle length which roughly corresponds to its resting length. When the muscle is either shortened or elongated, the maximum contractile force, that force correcting for any passive tensile component, is reduced. The general observations hold for amphibian [30] and mammalian muscle [18], isolated amphibian muscle fibres [218], and isolated human muscle [217]. Although Huxley and Niedergerke [134] commented that the force-length relationships found by Street and Ramsey were consistent with their hypothesis of muscle force being proportional to the number of interacting sites between the myosin rods and actin filaments, it was not until the work

of Huxley and Peachey [135] and Gordon and his co-workers [114] that this could be verified.

Huxley and Peachey [135] investigated production of force by isometric tetany in muscle fibres stretched to a length that would eliminate contractile filament crossbridges. By measuring striation and sarcomere distances, they found that in the passively stretched fibre, spacing in the middle sections of the fibre was greater than near the ends. Therefore in the elongated fibre, tension could still be produced by the sarcomeres situated away from the centre. Further, during contraction, the middle sarcomeres are stretched even more. To control this stretching, Gordon and his associates [114] employed a photoelectric device which monitored the distance of two gold leaf markers. Those were placed over a section of the fibre where the striation spacing was constant. When the fibre was tetanically stimulated, any disturbance in the distance between the markers caused a servo-motor to automatically adjust the position of the transducer-free tendon end. Thus striation spacing was preserved. Gordon and co-workers constructed the force-sarcomere length relationship showing that the optimum length for tension and most other points on the curve correlated well with structural indices reflecting the number of myosin and actin interacting sites.

The characteristic force-length relationship also appears to apply to some in vivo human muscles, the

quadriceps muscle group [121] and the biceps brachii [138]. However as the results of McComas and his associates indicate this will not always be so. In the case of the triceps surae muscle group, the greatest torque was produced when the ankle was very close to its maximum dorsiflexed position [227]. As a result, in the intact anatomic arrangement, the optimum position must not be assumed to be the same as the resting position. When the tibialis anterior was maximally excited, either voluntarily or by stimulation at 40 Hz, the optimum position for torque was near the middle of the range of motion [176]. At lower rates of stimulation, particularly 20 and 10 Hz, there was no longer a clear peak of maximum torque. A widening plateau became evident. This raises an aspect of muscle mechanics often overlooked. Observations of the behaviour of fully tetanized muscle may not be directly applicable to most situations in which skeletal muscle is activated. Many limb muscles are actually complexes of several muscles and force-length curves will depend on the relative activation of each of its components. Furthermore, muscles are generally activated to perform at stimulation rates far less than their tetanic frequency, i.e. at 5 - 20 Hz.

Rack and Westbury [215] subdivided the ventral nerve roots of cat soleus into five bundles of motor neurons and stimulated them in a rotational order. The optimum length for force production was shifted to longer and longer muscle

lengths as the rate of stimulation was decreased from a tetanizing frequency of 50 impulses/sec to 3 impulses/sec. The maximum tension was reduced with the slowing of the stimulation rate but the slow levels were more representative of most muscle behaviour. As the muscle was shortened, progressively more rapid firing frequencies were required before any isometric force was produced. Graphs of stimulation rate and force show that all frequencies were able to produce large gains in tension with muscle elongation, however for each frequency, the steep portion occurred at different muscle lengths.

Interestingly, two reports contain figures which demonstrate the other possibility compared to the results of Rack and Westbury [215]. (1) Ralston as his co-workers [217] predicted the effect of fatigue on the maximum force-muscle length relationship. They proposed that the optimum muscle length would remain unchanged, and that a given level of fatigue would simply decrease the maximum force at this position. At all other muscle lengths, the maximum force would be decreased by the same proportion as at the optimum length. For a greater level of fatigue, force again would simply be the scaled down version of the original relationship. Unlike Rack and Westbury [215], Ralston's group [217] expected all the curves of force to converge at the same maximum and minimum muscle length. Rack and Westbury stimulated all the muscle fibres at low frequencies. Ralston

considered all the muscle fibres but they were weakened by fatigue. (2) Houk and his associates [129] maximally stimulated three separate portions of the ventral root of in-situ cat soleus and measured the force response of the excited motor units. Despite the different condition, their data are the same as the theoretical curves of Ralston's group. Optimum length was the same but the level of force for each muscle part at the different lengths was reduced in proportion to the maximum force difference. These reports highlight the complexity of predicting submaximal force on the basis of the maximum force-muscle length relationship.

Studies of the mechanical behaviour of skeletal muscle have prompted similar types of investigations on the respiratory muscles. Skeletal muscle is under voluntary control but the respiratory muscles are subject to additional autonomic influences, both excitatory and inhibitory in nature [109]. By transferring principles developed from limb muscle experiments, we have the basis for understanding the muscular control of breathing.

Gesell and his associates [106] measured the activity of individual motor units of dog diaphragm to investigate the gradation of force during inspiration. In the eupneic and chemically stimulated breaths studied, both increased firing frequency and motor unit recruitment contributed to the inspired volume. The general observations were best illustrated by two of their figures. Figure 2 of

their report is a schematic representation of two inspirations. In the eupneic breath, the EMG of 28 different widely spaced motor units was recorded. These were recruited in a fairly linear fashion over the time of the breath. Those motor units active earlier in inspiration increased their firing frequency steadily until the appropriate volume was reached. Therefore at the start, there were few units active and these contracted slowly. At the end, more units were involved and all fired more quickly. A hyperpneic breath simply recruited more fibres at a faster rate and these increased their contraction frequency more rapidly.

Figure 5 of their report considers 50 increasing hyperpneic breaths. Tidal volume increased in a concave-curvilinear manner over time. Three muscle fibres of different motor units were isolated. When tidal volume increased from 50 to 70 ml, only one of the units was active, but it increased the number of contractions gradually over the 7 inspirations from approximately 6 to 13 times/breath. Then the second motor unit was recruited at 2 twitches/breath, it gradually increasing in firing frequency to 11 over the next 10 breaths while tidal volume rose to 95 ml. During this time the first motor unit reached a maximal twitch number/breath of 16. To increase tidal volume over the succeeding 15 breaths to 100ml, a third motor unit was recruited which contributed at first 3 contractions, then

more at 8 impulses/breath. Meanwhile the second unit added 2 more twitches to each inspiration. Over 15 breaths from the time of their initial recruitment, these motor units increased their firing frequency from approximately 4 to 8 Hz. The authors summarized that although the activity of any single motor unit did not reflect the force of the whole muscle, at these low excitation rates the total twitches of all motor units sampled correlated with muscle effort, in this case, the breath volume.

The observations of Iscoe and his co-workers [137] are somewhat at variance with those of Gesell. They recorded the activity of phrenic motor axons in anaesthetized cats. As Gesell and his co-workers reported, different units were recruited at different times during inspiration with the order stable even during hypercapnia. This correlated well with the time of activation during an occluded breath. Once recruited, there was a general increase in that unit's firing frequency, the mean peak frequency being 13 Hz. In contrast, unit recruitment did not occur steadily throughout the inspiration. By the time only 30% of the inspired duration had elapsed, 73% of the monitored units had already been activated. There was no recruitment beyond 80% of the tidal volume. Thus force would have been increased primarily through increased firing frequency. This is consistent with the work of Milner-Brown and associates [188]. When the airway was occluded, the

units recruited later in the breath increased frequency more quickly in relation to the rising alveolar pressure than those activated early. Iscoe and his associates noted that for greater force, contraction frequency may be more important than recruitment or that extra units were not required if the later recruited units added sufficient pressure. In attempting to explain the difference in reference to the report of Gesell, Iscoe's group suggested that they may not have sampled all motor units and possibly missed recording from phrenic motor neurons which are generally recruited at higher lung volumes.

Although not directly applicable to the present discussion, it is interesting that several groups of investigators have attempted to assess the output of central respiratory control from measurements related to the electrical activity of respiratory muscles or phrenic nerves proposing that the two should be related through tidal volume [143]. Eldridge [88] observed in cats that the peak rate of the integrated phrenic neurogram was highly correlated with the pressure produced by the respiratory muscles over the first 0.1 sec of an occluded breath. The latter was assumed to be a potential mechanical index of controller output.

Similar to other skeletal muscles, the force-frequency relationship of the human diaphragm [16,199] and sternomastoid [198] has a characteristic S-shape. Tension begins to asymptote with stimulation frequencies of

approximately 50 Hz.

As was indicated earlier, the diaphragm is the only respiratory muscle in which it is possible to measure its force alone, that as Pdi. Static alveolar pressure, which is a reflection of Pmus, results from the net pressure created by all the muscles participating. "Net" pressure has been used to allow for the possibility that some muscles may behave as antagonists for inspiration. (Even the diaphragm, if taken to its limit in the caudal direction, can compress the rib cage [191].)

It would still be expected however that some mechanical indicators of respiratory muscle effort should be related to myo-electrical activity in the manner shown for other skeletal muscle. Campbell [45], using a qualitative description of the intensity of the EMG on record, described manoeuvres of the respiratory system which were associated with greater EMG in respiratory muscles. These included increasing tidal volume, and graded inspiratory and expiratory static pressures.

In probably the first report of quantified EMG of the respiratory muscles, Raper and his co-workers [219] examined the behaviour of the accessory muscles. As lung volume was increased and held with an open glottis, there was a linear increase in EMG of the scalene and sternomastoid. The increase was accentuated when volume approached the upper 25% of vital capacity. The same curvilinear

relationship was observed during static inspiratory efforts. At approximately -50 cm H2O, the EMG increased more sharply. The maximum amount of EMG was produced at total lung capacity. These observations are therefore consistent with the relationship of EMG and force seen in skeletal muscle as was discussed earlier.

To overcome the difficulty of assessing the role of motor unit recruitment, changes in firing frequency, and duration of the active state, Viljanen [258] utilized an EMG technique described by earlier investigators. The number of action potentials (N) were counted from amplified EMG records obtained from surface electrodes. These were situated in the sixth intercostal muscle space near the right mid-clavicular line. (In preliminary studies, the surface EMG agreed well with that from needle electrodes.) Indices of work were calculated using muscle pressure as the sum of the elastic recoil pressure of the relaxed respiratory system, and the dynamic pressure needed to overcome the flow resistive and inertial forces of gas and the lung. N was linearly related to total mechanical work ($W = \int P_{mus} \cdot dV$) counted over the one-third second interval at the end of inspiration, up to breaths of 2.7 l. The total N was similarly linearly related to power calculated over the first one-quarter second ($W = \int \dot{W} \cdot dt$). The relationship between alveolar relaxation pressure and N counted for one-quarter second, four seconds after the breath, was also a straight

line. Probably the most significant finding was that N matched the impulse of pressure ($I = \int Pmus \cdot dt$) for the same one-quarter second interval. If I and N were measured several times during a breath, they fitted the same straight line. Different breaths always produced straight lines but their slope varied. It was suggested that the respiratory centre could determine in advance of the breath which muscles will participate. Once the muscles are recruited, their contribution remains proportional to the load as evident by the slope. Careful delineation at the start of the breath would offer more details of muscle recruitment and recording the EMG of other muscles could further our knowledge of proportional contribution.

In the report of Rahn and associates [216], the maximum static inspiratory pressure was shown to decrease alinearly as lung volume was increased. Most of this reduction was accounted for by the elastic recoil of the respiratory system. When calculated as Pmus, maximum muscle force still decreased though less dramatically. The authors suggested that this might be due to the reduction in tension obtained with a shortened muscle. (Maximum transdiaphragmatic pressure also decreases with volume [187]). As lung volume increases, the diaphragmatic dome descends thus shortening muscle fibre length. The external intercostals pull the ribs closer to each other while the scalenes and sternomastoid lift the thoracic cage from above. It was also

the first study suggesting that maximum Pmus expresses the pressure reserve of the respiratory musculature.

Campbell [45] however differed with their explanation proposing that other events, primarily of a non-respiratory nature, could create thoracic pressures far in excess of those volitionally generated. Inhibitory reflexes, in the lungs or viscera, but not in the chest wall, probably exist which limit the static tension each muscle will produce. Furthermore, we are not able to assess the mechanical influence of antagonist muscles during an inspiratory manoeuvre. Therefore the pressures available for measurement only reflect the net pressure. Electromyographic investigations have detected strong abdominal muscle activity at high lung volumes which could presumably restrict the extent of inflation [43]. Despite such evidence, respiratory muscle force does seem to be limited by some factor which expresses itself through lung volume and results from animal experiments strongly implicate the muscle length-tension relationship.

Marshall [177] stimulated the phrenic nerve of anaesthetized animals with a constant intensity which only allowed lung volume to change over the range in which its pressure-volume relationship was linear. When elastic inspiratory loads were added while the stimulus was the same, intrathoracic pressure increased but the volume inspired was decreased. A series of increasing loads showed

the pressure increase and the volume decrease to follow a linear pattern. This same negative relationship was observed when the stimulus was increased in intensity except that it intersected the pressure and volume axes at higher values. The addition of resistive loads caused larger intrathoracic pressures at the beginning of the breath, but these returned to normal when the full tidal volume was reached. These results indicated that at a given level of excitation, the diaphragm performed most efficiently when the volume change and pressure change were intermediate. As mechanical work is the product of pressure and volume, a large pressure and small volume or a small pressure and large volume produce less work. If lung volume was first mechanically increased, the electrophrenic stimulus produced smaller changes in the breath size and intrathoracic pressure.

Marshall's analysis emphasized the length-tension relationship and Laplace's law. Assuming that the diaphragm's resting position places it at its optimum length for force production, artificially increasing lung volume would flatten the diaphragm, decreasing the length of its fibres and shifting it away from its maximum point of tension. At the same time, it would produce less transdiaphragmatic pressure according to the Laplace law ($P=2T/r$ where P=transdiaphragmatic pressure, T=tension of the diaphragm, and r=radius of curvature). Even if diaphragm

tension could be maintained, maximal pressure would still change in an inversely proportional manner with r, the r increasing with the flatter muscle position.

Evanich and associates [90] investigated the effect of stimulation frequency on the diaphragm's ability to produce pressure when it changed length. In anaesthetized cats, both phrenic nerves were stimulated at rates between 5 and 50 Hz. Intratracheal, esophageal and gastric pressures increased alinearly with increasing stimulation rate. The tension response typified that of other skeletal muscles, a steep rise in tension over the moderate stimulation frequencies generally seen in spontaneously active phrenic motoneurones, then a gradual asymptote. The difference in pressure between the lowest and highest frequency was 10 and 6 cm H2O for intratracheal and esophageal pressure respectively, but only 4 cm H2O for gastric pressure. At any muscle length shorter than at the end expiratory position, the pressure at every frequency was less than that observed for the control length. The shorter the length, the more exaggerated was the effect. Lengthing the diaphragm by decreasing lung volume below the relaxed end expiratory position, augmented the diaphragm's ability to produce pressure at any stimulation rate. To illustrate the magnitude of the effect, at 20 Hz, the transdiaphragmatic pressure at lung volumes 50 ml above the end expiratory position, at the end expiratory position, and at 50 ml below the end expiratory position,

was 4.5, 7, and 10.5 cm H2O respectively. At 50 Hz, they were 8.5, 13, and 21 cm H2O. Thus the diaphragm in the supine cat at the end expiratory position would not appear to be at its optimum length and by altering length through changes in lung volume, "gain", that ratio between stimulation intensity and force output, can be modified.

Kim and co-workers [149] studied the relative influence of changes in muscle length and the radius of curvature on the diaphragm's ability to produce pressure. In an open-chested dog preparation, they initially tested the precision with which diaphragm tension could be measured by recording from miniature strain-gauge arches sutured to an in-situ slip of muscle. Force transducers were fastened to a muscle strip encompassing the same slip simultaneously. Muscle length was derived from markers. Active tension was produced at muscle lengths ranging from 40 to 150% of the in-situ resting length. The latter was defined as that distance at which passive tension first appeared. At 125% of resting length, maximal tension was produced. (Most other skeletal muscles, having their optimum position for tension near the rest length, fail to produce any force at 60% of this distance. Thus the diaphragm appears to have a broader effective length range.) Subsequently, with the arches sewn into visceral segments of the diaphragm, tension, esophageal pressure, and lung volume were measured during maximal bilateral phrenic stimulation. The radii of curvature in the

Laplace law could now be determined. In these experiments both esophageal pressure, which is the same as transdiaphragmatic pressure since the abdomen was open, and diaphragm tension decreased similarly as lung volume increased. The calculated effective radius of curvature was relatively constant from -400ml to +600ml lung volume with respect to the end-expiratory position. At high lung volumes, the radius of curvature actually decreased which is directly opposite to what Marshall [177] predicted. Functionally, the optimum muscle length for pressure is less than that at the end expiratory lung volume position in the supine posture and probably is very close to the residual volume configuration. The lack of change in the effective radius of curvature suggests the relative mechanical insignificance of Laplace's relationship compared to muscle length alterations. However, due to the open abdomen in these experiments and the role of abdominal pressure [111], and the bucket handle movement of the rib cage during breathing, it is still inappropriate to completely dismiss the Laplace law at this time.

Grassino and his collegues [117] explored the length-tension relationship of the diaphragm in man utilizing magnetometers [182]. These allow measurement of any linear displacement occurring in a defined magnetic field, in this case the anterior-posterior motion of the rib cage and abdomen. According to Konno and Mead [152], these

diameters are closely related to the volume change in their respective compartments. Grassino and associates [117] proposed that although the diaphragm shortens during inspiration, the extent could be defined more precisely by the increase in the anterior-posterior diameter of the abdomen. (Since the abdominal contents may likened to an incompressible bag of water, any descent by the diaphragm expands the anterior abdominal wall forward via pressure on the viscera. Thus an increasing abdominal anterior-posterior diameter reflects diaphragmatic shortening while a decreasing diameter indicates lengthening. At any given lung volume, a number of different chest wall configurations are possible. The extremes would be a large rib cage diameter with a small abdominal diameter and a small rib cage diameter with a large abdominal diameter.) Static submaximal and near maximal transdiaphragmatic pressures were measured while the subject maintained different chest wall configurations at different lung volumes. Maximum transdiaphragmatic pressure decreased with increased lung volume but in a more organized manner when considered in terms of abdominal diameter. In some manoeuvres, even though lung volume differed by a litre, maximum pressure was very similar if diaphragm length was the same. For moderate static inspiratory efforts at a given length, diaphragm EMG was linearly related to the transdiaphragmatic pressure. Near the maximal intensities, the EMG increased more rapidly. Muscle length also

influenced the EMG. For a given level of pressure, a long diaphragm required less EMG, a shorter diaphragm, eliciting more EMG. Therefore the "gain" of the system appears augmented when the diaphragm is situated higher in the thorax.

II.C. CURARE AND SKELETAL MUSCLE

In this section the nature of curare's effect on skeletal muscle will be discussed. A general overview of neuromuscular transmission will be presented which will then be followed by a more detailed account of the relevant literature on curare's paralyzing effect.

It is interesting that it was through the use of curare that physiologists began to elucidate the manner of electrical transmission between nerve and muscle. Bernard, in the 1850's, reasoned that local peripheral events were responsible for curare's paralyzing effect when muscle was observed to respond to direct electrical excitation but not when the motor nerve was stimulated. Twenty years later, DuBois-Reymond suggested that it was not necessary to invoke a direct flow of current from nerve to muscle to explain excitation. Chemical transmission could occur between the two organs which would then cause muscle to generate an electromotive force.

When an action potential reaches the neuromuscular junction, local depolarization allows the influx of calcium ions into the neuron. These stimulate vesicles concentrated

at the terminal to release acetylcholine, estimates indicating a calcium:vesicle ratio of 4:1. Most of the acetylcholine is produced in the axoplasm of the nerve terminals and then concentrated in the synaptic vesicles. Following its release from the pre-synaptic membrane, a process also requiring calcium, acetylcholine diffuses 200Å across the synaptic cleft. The postsynaptic region is an enlargement of muscle fibre sarcoplasm and is characterized by numerous junctional folds. It is specialized for its function being electrically inexcitable but, containing approximately $5x10^7$ receptors. The acetylcholine-sensitive receptors are situated on the crests of the folds. Some of the diffusing acetylcholine will be rapidly hydrolyzed by acetylcholine esterase or washed out of the cleft, but much of it will be used to form transmitter-receptor complexes. If the active unit of the receptor is in the excitable state rather than in the desensitized form, the binding of 2 acetylcholine molecules cause the receptor to change its structural geometry. The local post-synaptic membrane permeability is then altered and rapid ionic movement through ionophores, lasting only about 2 msec, leads to a reduction in the potential difference across that membrane. If the potential, called the end-plate potential, of the entire end-plate region reaches the threshold, approximately 10-20 mV less than the resting potential, full depolarization occurs with subsequent propogation of an action potential along the

sarcolemma.

In the absence of motoneurone excitation, electrical activity at the neuromuscular junction can still be measured. With intracellular electrodes, Fatt and Katz [92] observed "miniature end-plate potentials", low amplitude (approximately 0.4 - 1.0 mV), randomly occurring, depolarizations occurring at the rate of about 1/sec but only in the end-plate region. Subsequent studies by DelCastillo and Katz [73] suggested that each miniature end-plate potential was due to the spontaneous release, probably from one presynaptic vesicle, of a quantum of acetylcholine consisting of several thousand molecules. The amplitude of neurally evoked potentials seemed to verify this, presenting statistically in multiples of the miniature potentials [34].

Although the acetylcholine receptor is quite specific for the neuromuscular transmitter in-vivo, other agents such as nicotine and muscarine can also stimulate it, while a second group can cause inhibition. Curare belongs to the latter group, competing with acetylcholine for the two subunits on the nicotinic cholinergic receptor. To inhibit the receptor's conformational alteration normally induced by acetylcholine, curare needs to bind with only one of the two receptor sites. As the total number of open ionophores is reduced, smaller miniature end-plate potentials are produced. As long as the end-plate potential fails to reach threshold, the muscle fibre is unable to

develop an action potential. This describes the conventional thinking, but because there are acetylcholine sensitive areas on the motor nerve terminal, curare may have a pre-junctional influence also. For instance, Hubbard and Wilson [131] suggested from the run-down of the end-plate potentials that curare reduces the acetylcholine quantal content.

This property of preventing contraction has made curare, among other muscle relaxants, therapeutically valuable. Two prime examples are in the facilitation of abdominal surgery and laryngoscopy for which total paralysis is induced. However, in the condition of submaximal neuromuscular blockade (SMNB), our interest is in the remaining muscle function.

The extent of impairment of muscle function by interfereing with neuromuscular transmission was carefully analyzed by Paton and Waud [208]. In cat leg muscle experiments, they measured the amount of agonist (e.g. succinylcholine) required to produce a given mechanical or electrical response in the absence and presence of a competitive neuromuscular inhibitor (e.g. curare). Twitch height was maintained at control levels until approximately 70-80% of the acetylcholine receptors were occupied by the antagonist. As the fractional occupancy increased, the twitch was gradually reduced until at 90% receptor block, muscle paralysis was complete. The implications of these results were

described by their iceberg analogy. At low concentrations of competitive neuromuscular blockers, a significant number of receptors may be occupied but their is no measurable decrement in muscle function. The events are still confined to that portion of the iceberg below the water surface. At about 75% of receptor occupancy, the first evidence of block appears. Muscle function fails completely when 90% of the receptors are inhibited. This range from threshold block to complete block represents the tip of the iceberg, but it is achieved by manipulating only 15% of the total number of receptors. It would seem that the neuromuscular junction is a very sensitive system, however it must be emphasized that 75% of the receptors were first required to be inhibited before any effect was noticed. In other words, there is a substantial "margin of safety" for transmission. The findings indicate that in order to produce a normal response, under the conditions of 1 stimulation/10 sec, either only 25% of the raceptors available were required or, that the output of acetylcholine was four times in excess of the minimum amount needed to cause depolarization of a particular muscle fibre.

It is not surprising therefore that light levels of curarization are difficult to assess. Traditionally, the development of total block in a proportion of the motor end-plates has been studied by recording the amplitude of the compound action potential and/or the mechanical response

of a muscle during electrical stimulation of its motor nerve [124]. Stalberg and his associates [244] have improved the analysis, utilizing a multi-electrode needle to record single muscle fibre action potentials from voluntarily activated human muscle. They calculated the "jitter", which was the variability in the time interval between the action potentials of two muscle fibres belonging to the same motor unit. This reflects the instability at the end-plate. Under typical control conditions, the spike interval would be in the order of 500 usec. A possible reason for the interval is the difference in the conduction time from the motor axon branching point to the recording site along the two muscle fibres. The normal jitter ranged from 10-40 usec. At two levels of curarization not detectable from the evoked surface electromyogram, even though diplopia was present, the jitter increased first by 2-7 usec, then was prolonged to maximal values of 138 usec. The mean inter-potential interval changed by less than 100 usec and 500 usec respectively during the two curarization levels. These observations were recorded while the firing rate of the extensor digitorum communis muscle was maintained between 8-15 Hz. The jitter increase appeared greater for those pairs of potentials that had high jitter values before curare was administered. When the jitter exceeded 80 usec, complete block of the second potential and an irregular firing frequency were observed. Computer simulations

subsequently suggested that the variations in the jitter following curarization could be explained by changing rates of rise of the end-plate potential to the action potential firing threshold and/or low frequency fluctuations in the level of the firing threshold itself.

Due to the necessity of monitoring the extent of paresis during surgery, the anaesthesiological literature provides an abundance of information pertaining to the measurement of EMG and force during curarization. Unfortunately, much of it is descriptive, with only few reports proposing any physiological mechanisms.

In an uncurarized muscle which has been maximally stimulated with a single shock, the twitch tension after a brief period of tetanization can be up to 200% of the level before tetanization [52]. This "post-tetanic potentiation" occurs without any alteration in the amplitude of the evoked muscle compound action potential [132]. As the observed action potential implies full excitation of the same numbers of muscle membranes, the potentiation is most likely due to an augmentation of the "active state" of the contractile elements. Post-tetanic potentiation has also been demonstrated in human muscle systems [256]. When neuromuscular transmission is inhibited by curare, the single shock produces a depressed tension and compound action potential compared to control, with the former being more affected. Following 5 sec of tetanization, the tension and compound

action potential are increased when evoked by the same stimulus [89]. The potentiation may last from several seconds to occasionally for several minutes [133]. Depending on the extent of the original block, these amplitudes may approach the pre-curare level but will never surpass it. Before the tetanus, curare reduces the "margin of safety" therefore the decreased number of transmitter-receptor complexes at each motor end-plate may not be sufficient to depolarize the particular muscle fibre. Only those fibres stimulated, contribute to the now reduced compound action potential and twitch. The tetanus however stimulates the synthesis and mobilization of acetylcholine which continues into the post-tetanic period. Consequently, the quantal content is increased [166] so that more end-plate potentials will reach the firing threshold and produce "post-tetanic facilitation". An increase in the calcium content at the nerve terminal seems to explain this observation [147]. In the absence of curare, because the margin of safety is not compromised, the augmented acetylcholine availability does not add to either the evoked compound action potential or the twitch tension.

The increased acetylcholine synthesis does not occur immediately at the start of tetanus, nor is it immediately available. From the depression observed in the amplitude of intracellularly recorded post-synaptic end-plate potentials and the resultant calculation of quantum content, the rapid

stimulation of the motor axon is thought to first deplete the store of accessible transmitter at the nerve terminal [36]. At a frequency of 30 Hz, this occurs after approximately 300 msec. On high speed records, the amplitude of both the compound action potential and tension show "fade", with reductions of approximately 10% when compared with the first twitch. The mechanical records are difficult to interpret simultaneously with the EMG. Tension responds more slowly than the electrical events therefore an average is produced over this early period. During curarization at a level which reduced the maximal thumb twitch tension by 80%, fade depressed the EMG and tension amplitudes by 81% and 31% respectively [89]. The EMG appears to be a more sensitive indicator of neuromuscular block because during recovery from curarization when the twitch tension is still reduced by 20%, the tension fade is insignificant, again probably due to internal damping, yet the compound action potential during the tetanus is still decreased by 65%. Some recovery of both EMG and tension occur within seconds as the tetanus continues due to transmitter mobilization. At the maximum curarization level studied, post-tetanic potentiation increased the EMG to 85% of the uncurarized value but the tension to only 43%.

The extent of fade is dependent on the stimulation rate. The more rapid the frequency, the more sensitive fade is for the detection of neuromuscular block. Stimulation at

100 Hz for example, can reduce tension by 50% within several seconds even though twitch tension would have indicated recovery from curarization [110]. Ali and co-workers [13], claimed that even greater sensitivity could be obtained from the "train-of-four", comparing the tension height of the fourth twitch to that of the first twitch elicited by 2 Hz stimulation of the ulnar nerve acting on the thumb. The fourth twitch decreases before the first just as in higher frequency tetanic fade. It has the advantages of producing separate responses at a rate which causes transmitter depletion yet prevents facilitation of acetylcholine production following neural activation.

The margin of safety concept offers one explanation for these observations. When all the receptors are occupied by curare, there is no evoked response of any type in the muscle. Allowing transmitter-receptor union equivalent to 10% of the total receptors, permits single depolarization of only some muscle fibres which in turn sum to produce a fraction of the control twitch tension. Some low amplitude multiple twitches may be seen. The twitch is restored when 20-25% of the receptors are unoccupied. During this recovery, a lesser number of fibres are capable of firing four times. The train-of-four ratio does not reach control values until 25-30% of the receptors are freed. High frequency stimulation rapidly depletes the acetylcholine stores and depolarization is inhibited in some fibres which

contributed to tension at the start of the tetanus. Therefore fade is observed. To eliminate tetanic fade at stimulation rates of 100 and 200 Hz, 50 and 70% of the receptors are required, respectively [262,264]. This model however does not account for the possible pre-junctional action of curare in these events, particularly since high rates of stimulation seem to reduce acetylcholine output and facilitate neuromuscular transmission failure [103].

Since the assessment of neuromuscular block can be best performed with low frequency stimulation, but high frequency can detect any residual effects, Gerber and associates [105], have devised the frequency sweep electromyogram. Over a period of 10 sec, the stimulation rate is increased exponentially from 1 to 100 Hz while the integrated electromyogram is recorded from needle electrodes. Following curare administration, the EMG amplitude for the high stimulation frequencies was reduced first, followed gradually by a decrease in the EMG pertaining to the low frequency segment. Recovery from curare occurred in the reverse order. Their technique is most interesting but these results must be considered with reservation. These observations are what might be predicted from motor axon stimulation, yet their report on methodology suggests direct muscle stimulation. No effect would be expected unless curare also influences events occurring after the initiation of the threshold end-plate potential.

There seem to be no reports of the effect of curare on the force-length characteristics of muscles except for the observations of Pengelly and Rigg [211]. From cat tibialis anterior muscle, force-length relationships were recorded with supramaximal and submaximal tetanic stimulation of the popliteal nerve. Submaximal levels were produced with reduced excitation voltage levels. The optimum muscle length$_o$ for force production was the same for all intensities of stimulation. As the voltage level was decreased, the muscle length at which just measureable tension could be produced, shifted rightward away from the short length control point and toward the longer lengths. When the peak force of a submaximal stimulus (at optimum length) matched the maximum tension reached during curare, the two force-length relationships were the same, that is, optimum length and the short length of zero force were unaltered. It is suggested therefore that curare does not change the mechanical characteristics of the remaining contracting fibres. Furthermore, since the maximum force produced during curarization is not proportionately reduced at all muscle lengths, short muscle lengths appear to accentuate the weakness. Consideration should be given to the method of submaximal stimulation employed which could be selective for motor units with lower firing thresholds.

Various objective methods to assess the degree of neuromuscular block in-vivo, as well as clinical

observation, have indicated that different muscle systems do not have the same sensitivity to an antagonist even though the circulating concentration of the blocker can be assumed to be constant throughout the body [113,141,242,268]. In man at least, small muscles are the first affected with rapid development of diplopia, and ptosis. Weakening hand, jaw, and facial muscles follow, succeeded by inability to lift the head and to swallow. Eventually, the respiratory muscles are affected. The particular reasons for this pattern remain unclear but differences in muscle biochemical properties, motor end-plates, motor neurons, local blood flow, and temperature have been repeatedly implicated.

Curiously however, the order of muscle weakness may not be the same in all animals. The report of Paton and Zaimis [207], which has stimulated much of our thinking of a differential muscle effect by curare, indicated that respiration was depressed at much lesser doses of curare than those required to depress twitch tension in cat tibialis anterior. This was not due to any pronounced effect on the respiratory centres as phrenic nerve root discharge was maintained. In cats, as well as monkeys, quiet diaphragmatic movements changed to a distinct thoracic pattern, which eventually recruited all the accessory respiratory muscles before ventilatory arrest occurred. The soleus required 50-70% less curare for abolition of the twitch than did the tibialis, suggesting to the investigators a similar

physiology for the respiratory muscles and the soleus, i.e. "red" muscles. When tetanus was induced during partial curarization, 20 Hz for 5 sec, the resultant tension showed a greater decrement than the decrease in the twitch tension would have indicated. For example, in tibialis, the tetanic/twitch-tension ratio was only 0.65 (a ratio of about 5 in uncurarized muscle). With greater curarization, the ratio was further decreased to 0.063. (In the soleus it was reduced from 7 to 1.) If the tetanic changes are a real phenomenon, it might also explain the ventilatory depression since respiration could be considered a tetanic activity.

Motivated by the report by Paton and Zaimis, Alderson and Maclagan [12] repeated their measurements but controlled for an effect of temperature. When cat diaphragm, tibialis anterior and soleus were at the same temperature, about 36 degrees Celsius, curare reduced the twitch tension of the tibialis and the single evoked action potential of the diaphragm by a similar amount. The block was much greater in the soleus. When limb muscle temperature was allowed to follow its natural course, approximately 3 degrees Celsius less and presumably similar to the conditions of Paton and Zaimis, the tension decrease was greatly reduced. It was almost totally abolished in the tibialis, and approximately halved in the soleus making the latter appear similarly affected as the diaphragm which was still at core temperature. The tetanus response was similar as

before, supporting the notion of respiratory muscle depression due to peripheral nerve-muscle factors. When the diaphragm was stimulated before curare administration at 20 Hz for 0.5 sec, the tenth evoked potential had a similar amplitude as the first. Shortly after an infusion of curare, the first evoked potential, which would have indicated a 60% block, was followed by successively smaller potentials until the last was barely detectable in spite of the constant stimulus. The tenth potential was still only 50% of the first after partial recovery from curare to within 30% of control. This "fade" of tetanic electrical response with curare was in marked contrast to the tetanic maintenance following decamethonium, a depolarizing neuromuscular blocker. There was no selective action among the respiratory muscles after curarization. The potentials in the diaphragm, and intercostal muscles at T5 and T10 were abolished within several breaths. Phrenic discharge was increased during and after this period which caused an increase in chest movement before paralysis without the recruitment of other respiratory muscles.

Ali and his co-workers [14], employed the "train-of-four" technique every 10 sec to compare the effect of curare on a peripheral muscle with those of several respiratory measurements. When the adductor pollicus train-of-four was reduced to 60%, vital capacity and maximal inspiratory pressure were significantly decreased to 91% and 70%

respectively. These increased to 97% and 82% when the train-of-four recovered to 70%. At this level of curarization the respiratory changes were clinically unimportant.

In anaesthetized patients, Lee [158] monitored the ability to breathe against an expiratory obstruction of 5 cm H2O. Following a single bolus of curare, expiration was quickly compromised, usually tens of seconds before any indication of thumb twitch weakness. Thumb twitch was present even during periods when assisted ventilation was necessary. Recovery of the expiratory muscles occurred minutes before the thumb twitch.

The margin of safety test has been applied to the diaphragm [263] and indicates a slightly greater neuromuscular reserve there than in peripheral muscles. The twitch tension was measured by applying a strain gauge to the freed costal insertion of the left hemidiaphragm. For a reduction of the twitch to one half, 8.3% more receptors needed to be occupied in the cat diaphragm compared to the tibialis anterior. In the dog, this was only 3% more. For full recovery of the twitch from curare in the cat, the diaphragm and tibialis anterior required 18 and 29% of the receptors to be freed, respectively. For the same response, in the dog, the values were 5 and 10%.

II.D. RESPIRATORY MUSCLE PARALYSIS

In this section, the effects of pharmacological paralysis of the respiratory muscles will be reviewed. The first part consists of those investigations utilizing the systemic introduction of a neuromuscular blocker. This affects all the skeletal muscles but as indicated earlier, the degree of paralysis does not appear to be the same among muscles, and is possibly not the same among the respiratory muscles themselves. The review is generally chronological to illustrate the progression of the observations of the submaximal condition. These studies are technically difficult. They require personnel trained in anaesthesiology, who have the additional capability of producing and maintaining a steady-state level of muscle weakness. Furthermore, the experimental measurements are becoming increasingly complex. Total respiratory muscle paralysis is considered in the second part. These are no less difficult for the subjects have no control over their involvement and must be mechanically ventilated. Finally are reported the observations of two investigations where local analgesia was utilized to block specific respiratory muscles.

II.D.1. Submaximal Paralysis

Rigg and his co-workers [221] investigated the ventilatory response to CO2 of curarized subjects. Neither mild paralysis, which reduced mean vital capacity, maximum inspiratory pressure and hand grip strength by 14, 19 and 55% respectively, nor moderate paralysis, which decreased the same indices by 34, 78 and 94%, had any effect on the response to increases in rebreathed CO2. The remaining respiratory muscle power therefore appeared adequate to meet submaximal ventilatory tasks.

Gal and Smith [99] assessed respiratory muscle function during different levels of submaximal neuromuscular blockade by stimulating ventilation with constant fractions of inspired CO2. For the control ventilatory value of 25 l/min, tidal volume was 1550 ml and respiratory frequency was 16/min. With each successive dose of curare, minute ventilation was maintained but the tidal volume contribution decreased and frequency increased. After the accumulated dose of 0.20 mg/kg, which reduced hand grip strength to 6% and vital capacity to 52% of control, tidal volume was only 1050 ml and frequency rose to 21/min. This alteration in

pattern substantially decreased the elastic recoil which the respiratory muscles needed to overcome on each breath while adding only small increases in flow and viscous resistance. If this had not occurred, an increasing share of the decreasing maximal muscle pressure available would have been used. The maximum inspiratory alveolar pressure at FRC was reduced by 63% to 24 cm H2O following the last dose.

Saunders and his associates [232] observed that during submaximal neuromuscular block, inspiratory capacity was reduced to a greater extent than expected, changing by an amount similar to the maximum inspiratory alveolar pressure change. The IC was predicted by first calculating the control maximum muscle pressure from the difference between the maximum inspiratory alveolar pressure and the recoil pressure of the total respiratory system. Next, over the vital capacity range, muscle pressure was reduced by 25 and 50% to produce two curves. To each of these curves, recoil pressure, assumed to be unchanged, was added. These resultant alveolar pressure curves then predicted the IC as that point when the muscle pressure during curarization was just able to overcome the elastic recoil of the respiratory system. For example, with maximum muscle pressure reduced by 75% at FRC, the IC would have been expected to be decreased by only 25%. Rather, they found IC to be reduced by the same amount as the maximum alveolar pressure. The other important observations were provided by magnetometry. During

inspiration to total lung capacity while curarized, the rib cage and abdomen essentially followed the same volume pathways as during the control period but the maximum level of rib cage expansion was reduced by 67% while the abdomen actually increased slightly. During quiet breathing, rib cage motion relative to abdominal motion was sharply reduced. Occasionally, there was even paradoxical motion, this occurring at the time of greatest muscle weakness. The chest wall configuration did not appear to be altered at the end-expiratory lung position. The most likely possibility to explain the difference between the predicted and actual results was suggested to be unequal paralysis among the respiratory muscles, agonists and antagonists alike. This could have disturbed the normal recruitment and coordination pattern. Therefore, "the translation of force into pressure at FRC may not reflect the ability to generate pressure at other lung volumes" (quotation from [232]).

Using a constant volume body plethysmograph, DeTroyer and Bastenier-Geens [65] studied the respiratory mechanics of seated normal subjects submaximally paralyzed with pancuronium. Functional residual capacity, vital capacity, total lung capacity, and expiratory reserve volume were reduced by 15, 10, 10, and 27% respectively. There was no change in IC, residual volume, airway conductance at specific thoracic gas volumes or the maximum expiratory flow in reference to the static recoil of the lung. The

inspiratory pressure-volume relationship of the lungs was unchanged but the expiratory lung compliance was reduced by 10%. Submaximal paralysis shifted the pressure-volume curve of the relaxed chest wall to a more positive level along the pressure axis by approximately 4 cm H20 thereby indicating a decreased tendency to recoil outward at low lung volumes. This was considered the most likely determinant of the decrease in the functional residual capacity.

In a subsequent investigation, DeTroyer and his associates [68] recorded the EMG of the respiratory muscles with concentric needle electrodes during submaximal neuromuscular block. They showed that when tidal volume was at any level up to 1 l, at a time when the vital capacity was reduced by 29% and the IC by 20%, pancuronium reduced the electrical activity of the parasternal internal intercostals, scalenes, and external obliques. The diaphragm EMG was increased which, together with the elevated abdominal pressure at any esophageal pressure, provided evidence for an increased diaphragmatic contribution during breathing. They suggested that this was possible if the diaphragm was more resistant to the effects of neuromuscular synaptic blockers than the intercostal/accessory muscles. Although it is difficult to dispute their overall conclusions, they fail to draw attention to the fact that the EMG's and pressures were recorded with the subjects in different postures, i.e. supine and sitting respectively. It is known that

position alters the mechanics of the respiratory system [9] and muscle activation [81,239].

Employing a technique of progressive partial curarization, Gal and Goldberg [100] studied the static and dynamic behaviour of the diaphragm while subjects were in the supine position. After accumulative doses of 0.05, 0.10, 0.15, and 0.20 mg/kg of curare separated by 7 min intervals, mean static maximal transdiaphragmatic pressure at e.e.p. decreased from approximately 122 to 112, 104, 75, and 52 cm H2O respectively. Proportional reductions were present at other lung volumes suggesting that normal length tension relationships of the diaphragm had not been altered. During IC manoeuvres, Pdi decreased from 49 to 45, 43, 39, and 28 cm H2O. The IC was unaffected until the third and fourth dose when it was reduced from 4.8 to 4.3 and then to 3.3 l. This was anticipated since at the curvilinear extremes of vital capacity, large pressures only produce small changes in volume. Curare had no effect on tidal volume or Pdi during quiet breathing. During a 12 sec maximum voluntary ventilatory effort, the calculated minute ventilation decreased progressively from 193 to 81 l/min, but only with the final curare dose did the Pdi increase in each breath fall significantly to 30 from 48 cm H2O. The control Pdi produced during IC and maximum voluntary ventilation represented approximately 41% of the static Pdi max at e.e.p.. This proportion gradually increased with curare

administration so that by the final dose, approximately 63% of the static Pdi max was developed. During quiet breathing, the proportion increased from 7 to 17%. The marked rib cage motion observed with the IC and maximum voluntary ventilation manoeuvres was not apparent after curare. Abdominal breathing remained the predominant pattern during a tidal breath. The suggested probable explanations for the progressive reduction in maximum voluntary ventilation were (i) increases in upper airway obstruction, and (ii) loss of strength and perhaps coordination of extradiaphragmatic respiratory muscles, both inspiratory and expiratory, forcing the diaphragm to assume a greater relative role.

In supine subjects curarized to graded levels of weakness, Gal and Goldberg [101] examined the relationship between respiratory muscle strength, an average of the maximal static inspiratory and expiratory alveolar pressure, and vital capacity. When mean respiratory muscle strength was reduced to 86, 71, 58, and 39%, the respective values for vital capacity were 100, 97, 85, and 66% of the control measurements. Since the two measures agreed according to calculations based on the muscle pressure available and the static recoil of the normal respiratory system, they suggested that the pressure-volume relationship of both lung and chest wall were not altered by submaximal paralysis. The IC, expiratory reserve volume, and maximum alveolar inspiratory and expiratory pressures also followed the

prediction, even though expiratory muscle strength was always reduced to a greater extent than that of the inspiratory musculature. The maximum lung recoil pressure of 14 cm H2O during maximum weakness was not significantly different from the control value of 11 cm H2O at a comparable lung volume. Lung compliance remained unchanged after curarization. The investigators raised the important issue of posture, indicating that IC may appear to be relatively well preserved compared to inspiratory alveolar pressure at FRC because the lengthened diaphragm, even when weak can overcome the very compliant abdomen.

In their subsequent investigation of the effects of curare in the supine position, Gal and Arora [102] compared the maximal static pressures with dynamic pressures and maximum air flow. Under the condition of greatest weakness, maximum inspiratory alveolar pressure at FRC was reduced to 42% of control. At the same time, alveolar driving pressure measured at mid-vital capacity during a forced inspiration was only decreased to 75%. According to the iso-volume pressure-flow relationship, the maximum inspiratory flow would have been expected to be decreased by a similar amount. However, a doubling of airway resistance, most likely in the upper segment (and possibly vocal cord paresis or relaxation of the tongue or pharyngeal muscle) reduced the flow to 41%. The increased resistance had little effect during forced expiration so that although maximum alveolar

driving pressure and static alveolar pressure were reduced to 32 and 21% respectively by curare, maximum mid-vital capacity expiratory flow only decreased to 85%. Expiratory flow is still effort independent in this volume range. The FRC did not change but residual volume was increased, rising from 21 to 29% of the control total lung capacity.

II.D.2. Maximal Paralysis

Van Lith and his associates [255] found that following anaesthetization and paralysis, total respiratory elastance (inverse of compliance) in the supine posture had decreased to 9.4 from the value of 11.8 cm H2O/l measured during the awake, relaxed state. Lung elastance was unaltered so all the change was due to a decrease in the elastance of the chest wall from 5.9 to 3.7 cm H2O/l. After light anaesthesia, and during apnea induced by hyperventilation to reduce interference from muscle reflexes, paralysis still reduced the total elastance from 9.4 to 8.3 in a different group of subjects. Assuming that the paralyzed measurements are the real physiological values, it seems likely that some involuntary expiratory muscle activity in the control situation is responsible for the difference in elastic recoil between the two conditions and must be considered when chest wall elastance is measured by the relaxation technique.

In anaesthetized, then anaesthetized-paralyzed volunteers studied in the supine position, Westbrook and his co-workers [265] found that mean FRC decreased from 3.08 to

2.38 l with anaesthesia but not further upon induction of succinylcholine paralysis. Static pressure-volume relationships for the lung and the total respiratory system were determined during the passive exhalation following mechanical ventilation to end-inspiratory pressures of 35-40 cm H2O. Lung recoil increased after anaesthesia from 2.8 to 12.8 cm H2O at 50% of control total lung capacity producing a similar increase in the recoil of the respiratory system. The addition of paralysis caused no other change. On analyzing the mechanical factors determining the FRC level, it was suggested that the anaesthetic reduced the outward recoil of the chest wall. Therefore, inward recoil of the lung was unapposed allowing FRC to decrease. The subsequent ventilation at low lung volumes produced a less compliant lung which in turn was possibly mediated by an alteration in the compliance of the lung's surface lining and/or atelectasis. The latter was probably less important since relatively large mechanical inflations did little to reverse the process.

Rehder and associates [220] determined if the frequent observation of a reduction in FRC in supine, anaesthetized and paralyzed man also occurs in the sitting position. Following measurements while sitting, the subjects were anaesthetized in the supine position and then returned to the control posture. Dynamic lung compliance was assessed after the lungs had been near fully inflated. The FRC was

measured by the open-circuit method of nitrogen washout. The breathing system had an end-expiratory threshold pressure of less than 1 cm H2O. Mean values for FRC did not change after induction of general anaesthesia, muscle paralysis, and mechanical ventilation. Lung compliance also did not change. It still appears that the reduction in FRC is related to the supine posture secondary to breathing at low lung volumes as Westbrook and associates later [265] suggested.

Froese and Bryan [96] radiologically examined the position and motion of the diaphragm of three subjects studied in the supine and left lateral decubitus position to determine the independent and combined effects of anaesthesia and muscle paralysis. During spontaneous ventilation under the awake and anaesthetized conditions, diaphragm motion occurred primarily in the dependent region. There, a smaller radius of curvature and an efficient development of tension for a unit of muscle length were thought to assist the diaphragm in overcoming the resistance exerted by the abdominal contents. Regional ventilation was assumed to be associated with local diaphragm movement. During anaesthesia and/or paralysis, the diaphragm assumed a more cephalad end-expiratory position, particularly in the lower region. The reduction in active tension of the diaphragm and possibly an increased abdominal muscle tone in the cage of anaesthesia alone were considered the most

probable contributing factors. The non-dependent muscle area, since it would be expected to offer the least resistance, was displaced most readily by mechanical ventilation during paralysis. Positive end-expiratory pressure, which would be theoretically capable of reducing the decrease in FRC with anaesthesia, was found to only displace the superior portion of the diaphragm towards its original position. This result likely fails to improve the ventilation of the dependent regions of the lung where alveoli with low ventilation/perfusion ratios would predominate.

Respiratory magnetometers were used by Vellody and co-workers [257] to determine the compliance of the rib cage and the diaphragm-abdomen in the relaxed compared to the paralyzed supine position. Anterior-posterior diameters of the chest wall were measured in response to a given static negative pressure applied to the body surface. Subjects were enclosed up to the neck. (The alveolar pressures were positive relative to the surface of the thorax therefore the procedure is similar to positive pressure breathing.) By using alveolar pressure as the reference, the resulting compliance of each component of the chest wall included a part from lung compliance in addition to their own elastic recoil. In 8 of the 11 patients, the diaphragm-abdomen was more compliant than the rib cage during awake spontaneous breathing. In 7 of the 11 patients, the rib cage was more compliant than the diaphragm-abdomen in the anaesthetized

paralyzed state. Following anaesthetization and paralysis, rib cage compliance increased in 9 of the 11 patients while in 8 of them, diaphragm-abdomen compliance decreased. With the increase in rib cage compliance after paralysis, it is possible that some "unrelaxable" rib cage expiratory muscle activity existed in the control state. Similarly, some diaphragm activity may have been present prior to paralysis which caused diaphragm-abdomen compliance to be spuriously elevated. Total respiratory system compliance was the same in the two conditions. The contribution of the rib cage to tidal breathing increased from 25% in the awake state to 48% with paralysis and mechanical ventilation. Possible explanations for this are the increased rib cage compliance and a more even distribution of the ventilatory pressure which had been selectively developed in the caudal pulmonary regions during spontaneous breathing.

Most studies of the effect of anaesthesia on the end-expiratory lung volume have shown that it is decreased, but any trapped gas behind occluded airways would have been undetected with the methods used. Hedenstierna and associates [125] therefore measured thoracic gas volume by body plethysmography and the region of any possible volume changes by recording various dimensions of the chest and abdomen. The FRC was decreased from 2.38 to 1.72 l following anaesthesia with no additional change with muscle paralysis. Paradoxically, no reductions were observed in

anterior-posterior diameters, circumferences, or cross-sectional areas of the thorax. The contribution of the rib cage to tidal breathing increased from 41% during the control period to 62% with mechanical ventilation following paralysis.

II.D.3. Specific Muscle Block

Following bilateral block of the 5th through the 11th intercostal nerves in semi-recumbent subjects, Jakobson and associates [139] observed no change in IC, residual volume, or the maximum inspiratory alveolar pressure performed at residual volume but maximum expiratory alveolar pressure at total lung capacity decreased from 113 to 94 cm H2O. The total lung capacity, forced vital capacity, and expiratory reserve volume were reduced by amounts similar to the reduction in FRC, approximately 270 ml. Lung compliance and airway resistance were unaffected. The abdominal musculature was weakened such that elevation of the trunk without assistance from the arms was just manageable. It was suggested that block of the intercostal nerves resulted in decreased outward recoil of the chest wall which allowed the FRC to fall. Inspiratory capacity was unchanged but the absence of part of the intercostal musculature and/or the mechanical fulcrum provided by the abdominal musculature, prevented the attainment of total lung capacity. Weakened intercostal and abdominal muscles were thought to also account for the reduced maximal expiratory pressure but the

subjects were still able to achieve the original residual volume. The inspiratory pressure at residual volume was maintained by the diaphragm, it apparently not requiring the lower intercostal or full abdominal muscles for this task.

The effect of extradural analgesia on respiratory function was studied in 30 patients by Takasaki and Takasaki [249]. Group 1 received cervical analgesia which affected the mean region of C4 - T7 as determined by a pin prick test 20 min after injection of mepivicaine. Thoracic analgesia was produced in Group 2 and affected primarily the region from T5 - L4. Among the main changes, vital capacity decreased in both groups with the 25% reduction in Group 1 being significantly greater than the 13% decrease of Group 2. In Group 1, the IC decrease was greater than in Group 2, 28% compared to 11%, but in Group 2 there was a significant reduction of 25% in expiratory reserve volume. For this measure, the 12% decrease of Group 1 was not significant. The 8% decrease in the arterial pO2 and the 3% increase in the arterial pCO2 of both groups following extradural analgesia was thought to be mediated primarily by the 21% reduction in tidal volume which decreased the minute ventilation. The forced expiratory volume in relation to the vital capacity was not affected but the maximum mid-expiratory flow rate decreased by 21%. These observations are consistent with the segmental location of principal inspiratory and expiratory muscles. Cervical analgesia had the greatest

effect on IC while thoracic analgesia decreased the expiratory reserve volume. It is perhaps surprising that all the lung volumes were preserved as well as they were in the two groups, however the decrease in neural function could not be precisely known since motor block need not always coincide exactly with the extent of the sensory impairment.

II.D.4. Summary

From these reports, it is concluded that inspiratory capacity during submaximal neuromuscular blockade is not reduced to the same extent as the maximum inspiratory alveolar pressure as Saunders and associates [232] originally reported. However strict comparisons cannot be made for their measurements have not been carefully repeated with subjects in the sitting posture. There is some evidence that regardless of the pressure available, the extradiaphragmatic muscles appear less active than the diaphragm following partial paralysis. With complete paralysis, many of the observations such as the increased rib cage motion during mechanical ventilation, can be explained by the relative compliance of the various parts of the chest wall. The functional residual capacity is reduced in the supine position but not in the upright posture.

CHAPTER III

METHODS AND PROCEDURES

III.A. SUBJECTS

The subjects were six healthy male individuals whose characteristics are shown in Table 1. Volunteer consent was obtained in accordance with the requirements of the Human Ethics Committee of the McMaster University Health Sciences Centre. Subjects 1 to 4 performed a control experiment one week prior to the curare experiment. They practiced the respiratory manoeuvres on several occasions before any experiments were performed. Subject 5 only did the curare experiment while subject 6 performed only the control experiment. The latter two were experienced in respiratory manoeuvres.

III.B. METHODS

Inspiratory and expiratory lung volumes relative to the relaxed end-expiratory position (e.e.p.) were measured with a water-sealed spirometer (Warren E. Collins, Inc., Braintree, MA) fitted with a 9-litre bell. A canister of carbon-dioxide absorbing soda lime was placed in the spirometer but the contained air was repeatedly mixed with room air. An oxygen-room air mixture was occasionally used to increase the volume of gas in the bell when complete recirculation was not possible. Two uni-directional rubber valves (Rudolph) were fitted to the tubing assembly which required threshold pressures of approximately 0.25 cm H20 to open. At the end of the tubing proximal to the subject, there were two aluminum valves. The first had a one-way tap allowing communication with the spirometer or complete interruption of air flow near the mouth. To it was attached a large rubber mouthpiece. The second valve was arranged to allow ventilation with either spirometer gas or room air. This minimized the amount of head movement that would have resulted if the mouthpiece was repeatedly removed and then put back into place. The dead space of this system was

approximately 125 ml. The subject wore a nose clip during all manoeuvres.

Mouth pressure (Pm) was measured since it represents alveolar pressure (Palv) under static conditions. Following interruption of air flow, Pm was transmitted by a section of tygon tubing (60 cm in length, 3.2 mm bore) to a Sanborn 267 transducer (Hewlett-Packard, Waltham, MA). The signal was then conditioned by a carrier amplifier (8805A Hewlett-Packard, Waltham, MA)

Esophageal pressure was used as an indicator of pleural pressure. A catheter-balloon system was constructed as described by Mead and co-workers [178]. A Hyatt thin-walled latex balloon (10 cm in length, 3.5 cm perimeter; Vacumed, Ventura, CA) was sealed over polyvinylchloride tubing (8Fr.; Argyle, Brunswick Co., St. Louis, MO) using Pliobond (Goodyear, Toronto, Ont.) and nylon thread. The polyethylene tubing (PE 200; Clay Adams, Parsippany, NJ) often used for measuring Pes was discarded for being brittle and prone to leaks at sharp bends. Throughout the section covered by the balloon, the catheter had numerous spirally arranged holes to transmit pressure. The other end of the catheter was fitted with a 3-way plastic stopcock (Pharmaseal Inc., Toa Alta, P.R.). Pressure was then recorded with a similar tubing, transducer and amplifier assembly as used for Pm.

A water-soluble lubricant was applied to the

deflated esophageal balloon and introduced through one of the nares following anaesthetization of the nasal mucosa with xylocaine ointment. It was then swallowed with a very small amount of water and placed approximately in the mid to lower third esophageal region. With the stopcock opened, the subject performed a Valsalva effort to deflate the balloon to a consistent level. Using a calibrated, double-ground glass syringe (Becton-Dickinson, Rutherford, NJ) fitted to a second stopcock, the balloon was expanded by introducing 6 ml of air through a port near the transducer. By then redrawing 5.8 ml, a bubble of air remained which is optimum for measuring the local pressure [186]. The vertical position of the balloon was adjusted slightly to produce a Pes as close as possible to -5 cm H20 at e.e.p. At the nares the catheter was fixed to the nose with surgical tape in order to prevent vertical movement of the balloon.

Gastric pressure (Pga) was measured to indicate the pressure on the abdominal side of the diaphragm. Although a balloon-catheter system identical to that used to measure Pes can be used, our modification allowed the simultaneous recording of diaphragm EMG. A balloon 6 cm in length and 16 cm in perimeter was made from condom rubber. It was sealed over a polyvinylchloride catheter containing spirally arranged holes under the balloon. A stopcock and tubing were fitted and then connected by means of a second stopcock to a third pressure transducer. This balloon was passed

through the nose, swallowed, and situated in the stomach. It was then inflated with approximately 25 ml of air, an amount which did not cause the minimally stretched rubber to produce a substantial positive pressure. The catheter was gently retracted until the balloon was felt to lie at the cardia sphincter. It does not pass this point in its inflated state. The subject then performed a maximal inspiration to pull down on the balloon and the exposed catheter was then taped to the nose to prevent vertical displacement.

By using the large gastric balloon, the cardia sphincter could be used as an anatomical reference point for the placement of the diaphragmatic electrodes in the esophagus. The electrodes consisted of two thin insulated strands of silver computer wire running inside the full length of the gastric balloon catheter. Approximately 20 cm of wire were exteriorized at the stopcock and balloon ends. The distal segment was stripped of its insulation and wrapped in tight coils around the catheter. This made a single 1 cm long electrode. The lower of the two electrodes was constructed to be as close as possible to the catheter-balloon thread junction, making it approximately 1 cm above the inflated portion of the balloon. The second electrode was separated from the first by 1 cm. This arrangement produced the best signal-to-noise ratio only after many combinations of number of electrodes, inter-electrode distance,

and distance from the gastric balloon were tested. The various preferences for diaphragmatic electrode construction have been reported [117,173,205,235]. In the ideal arrangement, the esophageal electrode would move in concert with the diaphragm. If tension is exerted on the gastric catheter at the nares with a small weight, the gastric balloon remains close to the cardia sphincter and the electrodes record from the crural part of the diaphragm. When the diaphragm descends, the stomach and gastric balloon are pushed downward and the electrodes move by the same amount that the diaphragm does [117]. The effectiveness of the weight is nullified when nose clips are used because the free sliding motion of the catheter is prevented. Since nose clips were necessary in these experiments, the gastric balloon was located where it would not impede diaphragm descent or distort its shape, yet still adequately record the electromyogram. Therefore, the end-inspiratory capacity position was selected. In this orientation, even the EMG of quiet breathing could be monitored.

The EMG of the other main respiratory muscles was recorded with pairs of miniature, bipolar, silver-silver chloride skin electrodes (Beckman Instruments Inc., Schiller Park, IL). The skin was rubbed vigorously with alcohol and a cotton swab until a tender erythema was produced. The electrode cups were level-filled with conductive gel and applied with adhesive collars. The width of the collars was

arbitrarily set to be the inter-electrode distance. The shielded 15 cm long leads from a pair of electrodes were tightly braided and the stripped ends pinched between the coils of spring terminals of differential pre-amplifiers (Holbrook Bioengineering, Hamilton, Ont.). These amplifiers were fastened with velcro to a jacket in a location close to the recording site. Following preamplification by 1000x, the signal was conditioned by a differential amplifier (Hewlett-Packard, 8801A) having a band pass of DC - 1KHz. Here it was amplified another 20-fold. The EMG was then passed through an instrumentation tape recorder (3960, Hewlett-Packard) to eliminate very high frequency signals, smooth-rectified, and recorded by a strip-chart polygraph (Hewlett-Packard, 7758A).

Myo-electric activity (mV) was assessed as only that signal above the electrical noise of the equipment and surrounding environment. All equipment was turned on, and with only background signal passing through the preamplifier, the zero baseline was established on the strip-chart. An 80 uV square-wave calibration signal of 1KHz was then delivered by passing 0.04 V from an oscilloscope (R564B, Tektronix, Beaverton, OR) through a 1/500 attenuator. The deflection on the strip-chart was marked along with the gain of all amplifiers. In this manner, all EMG could be measured in microvolts.

The diaphragm EMG from the esophageal electrode

required additional processing attention due to the electrical cardiac content which can be several times the amplitude of the EMG. An ECG gating system was constructed similar to one reported [201]. In the gating unit, a 10Nz filter blocked electrical motion artefact and the signal was led to channel 1 where it was delayed up to 25 ms. Channel 2 received the ECG signal obtained from bipolar leads in the CV5 configuration. The ground electrode was placed over the superior aspect of the left acromion process. The QRS complex of the ECG triggered a blocking mechanism in channel 1 so that all signals in that channel were gated off. The duration of gating normally has an upper limit of 0.1 sec. The diaphragm EMG was then smooth-rectified. This produces a recording in which small deflections toward the baseline represent the gated portions but the maximal amplitude is that of the rectified electromyogram (see Figures 5 and 6 of 8 channel recording).

One pair of surface electrodes were applied to the second or third intercostal space. The possible electrode sites were first palpated while the subject inspired deeply, concentrating to keep the neck and shoulders relaxed. At both the end-expiratory position and at inspiratory capacity, he then contracted the pectorals and muscles involved in motion of the jaw and neck position. The application site was chosen based on maximal palpable intercostal muscle contraction and minimal influence from the platysma and

pectoralis major muscles. Chest hair was shaved before the electrodes were applied. It is noted that the parasternal intercostal space may not be representative of all intercostal muscle activity [44,72,253].

The scalene electrodes were applied in the right posterior triangle of the neck in a vertical manner as described by Campbell [44]. The lower electrode was placed above the clavicle and behind the clavicular origin of the sternomastoid. Palpation and visual inspection ensured that artifact from the sternomastoid was minimal.

The final pair of EMG electrodes were situated over the right sternomastoid, midway between the clavicle and the mastoid process.

III.C. PROCEDURE

Subjects were instructed not to eat within 3 hrs before the experiment. They were seated upright in a high-back chair which was leaned slightly backward to provide relief for the postural muscles. Pillows were placed between the subject and the arms of the chair for lateral support and elevation of the upper limbs. The surface EMG and ECG electrodes were applied using methods described earlier. The esophageal and gastric balloons were swallowed at the end of the preparation period.

Subjects were informed of the nature of the experiment but not familiar with the details of the purpose. Four of the six subjects required practice to perform the various respiratory manoeuvres properly and reproducibly. Each visited the laboratory on at least three prior occasions over a period of several weeks. The practice sessions ranged from 1 - 3 hrs in duration. The subjects were instructed to produce static alveolar pressures which ranged from minimal to maximal intensity at different lung volumes. The pressure would be displayed on an oscilloscope (1308A, Hewlett-Packard) and when a particular target pressure was

reached, it was to be maintained for approximately 5 sec. It was also necessary to be able to completely relax the respiratory muscles at different lung volumes while the mouthpiece was occluded.

The experiment was divided into three segments. During the first and third parts, the static mechanical properties of the relaxed respiratory system were measured. The middle period was used to record the EMG of the respiratory muscles during the graded static inspiratory efforts.

Duplicate measurements of vital capacity were made. The pressure-volume (P-V) relationship of the total respiratory system was assessed according to a modification of the relaxation method of Rahn and associates [216]. The subject inspires to his inspiratory capacity, then momentarily holds that volume. The airway is then occluded and he relaxes completely. The pressure difference across the occlusion represents the combined recoil pressure of the lung and chest wall. The difference in pressure between the esophageal balloon and the atmosphere represents the recoil pressure of just the chest wall [4,150]. In these experiments, a 10 cm length of rubber hose connected the mouthpiece to the spirometer tubing. The occlusion was made manually with scissor clamps over that hose. The entire deflation P-V curve can be obtained by allowing brief leaks through the clamp while the subject remains relaxed. The volume changes are approximately 500 ml. On nearing the

passive end-expiratory lung volume, the subject actively expires to the residual volume and again relaxes against the obstruction. Several points can be obtained as he passively inhales from this position.

This manoevre also provides a correction factor with which abdominal pressure can be calculated from gastric pressure [2]. When the diaphragm is relaxed, its final position is determined according to the equalization of the pressure at its two sides. At rest therefore, the abdominal pressure just under the diaphragm can be assumed to be equal to the pressure in the thorax. The difference between the gastric pressure and the esophageal pressure during these relaxation manoeuvres and at e.e.p. must then be due to the tone of the stomach wall and a hydrostatic pressure in the abdominal cavity created by its contents.

The P-V relationship of the lung was to be measured by the quasi-static method. During a slow controlled expiration from total lung capacity, one momentarily holds particular lung volumes with the glottis open long enough to ensure zero airflow and the stabilization of the pressure record. This proved difficult for some subjects therefore the transpulmonary pressure, the difference across the lung (Palv-Pes), was measured during slight Valsalva manoeuvres against an obstruction [150]. Again deflation occurred from total lung capacity.

In the second part of the experiment, target

alveolar pressures were produced. When the subjects were at e.e.p. or guided to a particular lung volume above e.e.p., the airflow tap in the mouthpiece was closed. Alveolar pressure was monitored on an oscilloscope placed just above eye level in front of the subject. By watching the pressure deflection on the oscilloscope, he could produce any level of effort required. To allow the EMG to stabilize, it was important that the pressure be maintained with an open glottis for several seconds. This was more difficult as the effort approached his maximum ability. The aim was to record EMG as the subject moved through his inspiratory P-V map, i.e. producing different levels of pressure at different lung volumes. Each manoeuvre was performed twice. Since the smooth-rectified EMG can vary by up to 30-fold, a true random arrangement of the target pressures would have been very time consuming and increased the chances of recording errors, both being affected by the fact that the polygraph amplifier gains would have needed constant readjustment. Instead, a progressive plan was utilized whereby the targets ascended or descended the effort scale at one lung volume. When they were completed, the lung volume was increased or decreased by 1 l and the pressure order reversed. A rest period of 45 sec between manoeuvres was found adequate to prevent fatigue. If the lung and chest wall mechanics measurements are included, approximately 120 manoeuvres were performed.

The first of the two experiments for each subject was intended to explore a wide range of pressures and lung volumes so that interpolation between pressure and EMG could be kept to a minimum. Therefore, several pressures above one-half of maximum were aimed for, and the lung volume range included measurements at e.e.p. plus up to 3 l above this level.

On the second experiment day, the day of curare administration, the subject arrived at 0800 hrs in a fasting state. This day was usually 1 wk after the first experiment. The experiment was divided into two parts, the pre-curare control and submaximal neuromuscular block. The subject's posture was the same as during the first experiment with extra attention paid to lateral support of the thorax, arms and legs. The control pressures generally did not exceed one-half of maximum, except for the maximum itself, and no static pressure measurements were performed at e.e.p. plus 3 l. The rationale was that with curare, these higher levels would not be attained and they would unnecessarily prolong the experiment for the subject. As part of the control data on the second day, lung and chest wall mechanics were measured again in addition to the EMG. With a dynamometer (Lafayette Instrument Co., Lafayette, IND), hand grip strength was monitored so that peripheral muscle strength could be evaluated and indicate impending respiratory muscle weakness. The ECG was continuously

displayed and signals with the index finger were learned so that the subject could communicate with the supervising physician while curarized. Atropine sulphate (0.5 mg, Abbot Laboratories, Montreal, Que.) was administered intramuscularly near the end of the control period to reduce salivary secretions. Since these experiments were performed, we have become aware of a report noting increases in functional residual capacity and lung compliance following intravenous injection of 1.25 mg of atropine sulphate [64].

Following the control measurements, an infusion system was set up with an 18 gauge catheter (Argyle, St. Louis, MO) in a large superficial vein in the forearm. The aim was to produce a steady-state condition of submaximal neuromuscular paralysis so that the inspiratory capacity was reduced from 50 - 75%. This would be maintained for approximately one hour. Progressive paralysis was induced by the infusion of a dilute solution of curare (0.13 mg/ml) and sodium chloride (9 mg/ml, Abbot Laboratories). The original curare concentration was 3 mg/ml (Tubarine, Burroughs Wellcome Ltd., La Salle, Que.). Continuous measurements of hand grip strength, inspiratory capacity, and maximal static alveolar pressure dictated the amount of curare infused each minute. Two physicians were present during the curare experiment whose sole responsibilities were the safety of the subjects and the administration of curare.

III.D. ANALYSIS

The following were recorded on the strip chart: inspired lung volume relative to the end-expiratory position, static alveolar (mouth) pressure, esophageal pressure, gastric pressure, smooth-rectified diaphragm EMG with ECG gated, intercostal EMG, scalenes EMG, and sternomastoid EMG. Lung volume, Pm and Pes were analyzed directly from the records. For the P-V characteristic of the lung, Pl=-Pes when the glottis is open and lung volume held constant, or Pl=Palv-Pes when the airway is closed. (The latter requires a brief rearrangement of the pressure transducer connections.) For chest wall recoil, Pw=Pes during the static relaxed manoeuvre. For respiratory system recoil, Prs=Pl+Pw and should be the same as Pm. The difference between Pga and Pes when the muscles are relaxed, is deducted from all values of Pga to derive Pab. The sum of Pw, Pl and Pm calculate Pmus. Transdiaphragmatic pressure is calculated as the difference between abdominal pressure and esophageal pressure. The amount of EMG required during a static effort was taken as that level measured 1 sec after the target or maximal pressure was reached.

CHAPTER IV

RESULTS

IV.A. RESULTS OF CONTROL EXPERIMENTS

Figure 4 is a diagram of an inspiratory pressure-volume map. The line connecting the outermost points represents the maximum static alveolar pressure at different levels of lung volume. Volume ranges from the relaxed end-expiratory position, or the zero reference, to the inspiratory capacity. The intermediate positions are determined in litres above e.e.p. The points within the map are the target pressures. At each of these points, the electromyogram of the inspiratory muscles was recorded. Therefore the EMG has been controlled for pressure and volume which correspond to muscle force and muscle length.

Figures 5 and 6 are reproductions of actual recordings from one experiment. The responses to a target Pm of -40 cm H2O performed at a lung volume of 1 l above e.e.p are shown in Figures 5a and 5b. The pressure was less and the volume was greater in Figures 6a and 6b. It is noteworthy that: such submaximal inspiratory pressures are well maintained for several seconds; transdiaphragmatic pressure increases with the intensity of the manoeuvre and is generally constant throughout the effort; the small depressions

in the electromyogram of the diaphragm (Edi) are caused by the gating of the QRS complex of the electrocardiogram; the smoothed-rectified EMG requires a fraction of a second before reaching a constant level; the manoeuvres are reproducible; it is possible to record scalenes' surface EMG free of sternomastoid interference; and the EMG required to reach a specific inspiratory volume can be separated from that required to reach the target pressure as demonstrated by the diaphragm, intercostal and scalenes records in Figures 6a and 6b.

From such records, pressure-EMG graphs were derived as shown in the following figures. Since we use the convention practiced in respiratory mechanics [4,180] and EMG is the dependent variable, pressure is displayed on the abscissa. Due to wide variation in the magnitude of the rectified EMG among the various muscles and the subjects, no attempt has been made to derive mean values. However, particular patterns in muscle excitation were evident. These will be presented here and illustrated with specific examples. The results are shown in Chapter VII.

Examination of Figures 7a-d shows that over the full range of inspiratory mouth pressure in this particular subject, 0-105 cm H2O, all muscles generally produced more EMG as pressure was increased. Except with some very low levels of pressure, and then usually only at the end-expiratory lung position, in no subject were any of the muscles found

to be completely at rest during the manoeuvres. The rate of EMG increase however, appeared to vary depending on the muscle, the level of pressure, and the lung volume. Such comparisons can only be made by first noting that the range of EMG recorded was established by the muscle measured, the recording equipment, and full contractions which were elicited by maximal static inspiratory pressures and maximal inspirations. Therefore attention is drawn to the differences in the range of the ordinates of Figures 7a-d, being approximately 200, 25, 300, and 400 uV for the diaphragm, intercostals, scalene, and sternomastoid muscles, respectively. It would not be valid to make comparisons among the muscles of the absolute level of EMG.

Figure 7a relates the EMG of the diaphragm to the static inspiratory alveolar pressure. The open circles, the crosses, and the closed circles denote those manoeuvres performed at lung volumes of e.e.p., e.e.p.+2 l, and e.e.p.+3 l. At the e.e.p., the EMG levels over the low range of pressures appear to fall on a line that begins at the origin. There was approximately 30 uV of Edi for a pressure of -30 cm H2O. The EMG then shows a wide scatter of points for pressures ranging from -50 to -100 cm H2O.

To produce alveolar pressures at elevated lung volumes, greater muscle contraction is required. The set of EMG points for a volume of e.e.p.+2 l intersect the ordinate between 25 and 50 uV and then extend to the right. For the

same range of pressures to be performed at e.e.p.+3 l, the EMG values are collectively shifted upwards. A pressure of -30 cm H20 now produces approximately 180 uV.

The most striking difference between the other muscles, the intercostals, scalenes, and sternomastoid of Figures 7b-d and the diaphragm is that for the former group, the EMG points at e.e.p. do not extend from the origin. They generally follow a curvilinear pattern with a shallow slope over the range of low pressures and then a steeper increase as the pressures become greater. The intercostal muscles of this subject is a strong example of this pattern.

By displaying the force of respiratory muscle contraction as mouth pressure, useful information is hidden. The EMG points only take on meaning once a static pressure is produced. When esophageal pressure is used on the abscissa (Figures 8,9), muscle events occurring before the static pressure become evident. Figure 8 shows the EMG levels for the diaphragm at a lung volume of e.e.p. plus 3 l (symbol 3). This is the same data that was contained in Figure 7a except that it is graphed in relation to a single maximal EMG level recorded at the total lung capacity and compared to the esophageal pressure. It importantly illustrates the Edi as the expanding pressure on the lungs is increased by either static manoeuvres or increases in lung volume. To inflate the lungs to a volume of 3 l above e.e.p required 22 - 50% of the maximal EMG. Then, when the airway

was closed and a static pressure of -15 cm H2O was produced, esophageal pressure increased from 23 to 38 cm H2O and diaphragm EMG was elevated to 85% of maximum. The EMG response for manoeuvres performed at e.e.p.+1 l (symbol 1) are also shown in Figures 8 and 9. Esophageal pressure at the start of these static inspiratory efforts was approximately 8 cm H2O.

Figure 10 re-graphs some of the data of Figure 7b using esophageal pressure. Like the earlier plot, it shows the curvilinearity of intercostal EMG in response to increased effort. It also indicates that in this subject, the same low level of EMG was produced over an esophageal pressure range of 10 - 20 cm H2O irrespective of lung volume being at e.e.p. or e.e.p.+2 l. This was a general feature for the extra-diaphragmatic muscles for all subjects.

As initially illustrated for the diaphragm, when a particular alveolar pressure was produced at an elevated lung volume, the EMG was augmented. This pattern was seen in almost all of the muscles once the volume was increased by 2 l. Furthermore, it was evident at comparable esophageal pressures which would have tended to reduce the difference. This is because the static alveolar pressure was less at the elevated lung volume. The pattern is typified by Figures 11 and 12 in the scalene and sternomastoid muscles of subject 3 and is also evident in Figures 8-10. Figure 11 shows that at an esophageal pressure of -43 cm

H_2O, 11% of the maximum scalene EMG is produced while the lung was at e.e.p. The same pressure achieved at a 2 l greater volume elicited approximately 30% of the maximum EMG, over a doubling of the myoelectric activity. In the two cases where the augmented EMG with increased volume was less striking, one subject (subject 6) required to be at 3 l above e.e.p. before this pattern became apparent in the scalene and sternomastoid (Figures 13 and 14), while in the other, it never appeared for the intercostal and sternomastoid (subject 4). The two muscles of the latter subject seemed to follow a single curvilinear form with pressure increases, regardless of the lung volume.

Figure 15 (part of this data is contained in Figure 11) is redrawn in Figure 16 to illustrate the EMG of the scalenes in relation to net muscle pressure. The abscissa represents the muscle pressure required to first overcome the elastic recoil pressure of the lung and chest wall, and then to add the target alveolar pressures. The inclusion of chest wall recoil alters the position of the EMG data points compared to those of Figure 15 by displacing the curve representing the manoeuvres at e.e.p. to the left by approximately 4 cm H_2O. At this lung volume, chest wall recoil assists inspiration so the active muscle pressure is less than esophageal pressure by this amount. Those data derived at the increasing lung volume levels are shifted progressively to the right. For example, at e.e.p.+3 l, the

displacement of the same point from Figure 15 to Figure 16 is approximately 9 cm H2O. The net muscle pressure increases due to the increased tendency of the passive chest wall to favour expiration. The overall effect of using Pmus as the independent variable is to reduce the total area of the pressure-EMG diagram.

A useful representation of force of the diaphragm is transdiaphragmatic pressure (Pdi). Figure 8 is reproduced exactly as Figure 17 showing the EMG of the diaphragm at 1 and 3 1 above e.e.p. in relation to esophageal pressure. Next to it is Figure 18 which contains the same EMG data except that it is graphed against Pdi. The result is that all EMG points are shifted horizontally by an amount equal to the abdominal pressure during the manoeuvre. In this subject, the displacement occurs to the right. To illustrate, a static esophageal pressure in Figure 17 of -60 cm H2O elicits 75% of the EMG recorded at total lung capacity. This manoeuvre produced 43 cm H2O of abdominal pressure so that the pressure across the diaphragm is 103 cm H2O in Figure 18. In subjects who develop little abdominal pressure, the EMG relationship graphed against Pdi is relatively unchanged from that seen using Pes or Pmus.

IV.B. RESULTS OF CURARIZATION

To illustrate the effects of curare on muscle strength over the duration of the experiment, measurements from subject 1 are depicted in Figure 19. The general aim was to reduce inspiratory capacity to approximately 2.5 l and maintain that level of weakness for 40 min. An experienced anaesthetist administered curare intravenously in the manner illustrated by curve (*) which expresses the accumulative amount of curare given at periodic intervals relative to the total dose required for the experiment. A large dose is needed initially to produce the weakness. Subsequent small amounts are designed to reach and maintain the target weakness level. All experimental procedures were secondary to subject safety.

Diplopia and ptosis of the upper eyelids and jaw occur quickly followed by a reduction in hand grip strength (symbol +). Previous experience in this laboratory has shown that the near abolition of the hand grip is a good indicator of impending respiratory muscle impairment. In this subject, weakness was well maintained for approximately 1 hr during which time we measured the mechanical properties

of the lungs and chest wall, and recorded the EMG of the diaphragm, intercostal, scalenes and sternomastoid muscles in response to submaximal and maximal (symbol Δ) static inspiratory efforts. The mean inspiratory capacity (symbol ●) for the subject described in Figure 19 was 2.2 l. Figures 20 and 21 represent the time course for two less ideal experiments. Subject 4 required approximately 40 min to reach a steady level of weakness while subject 5, after having been curarized to the target level, regained his strength over the latter stages of the experiment although not completely. The results are shown in Chapter VII.

Table 2 contains the mean maximum inspiratory alveolar pressure measured at the relaxed end expiratory position and the inspiratory capacity for each subject. For the group, maximum pressure was significantly decreased to 38% of control ($p<0.001$) and inspiratory capacity was reduced to 68% ($p<0.001$). The former was affected to a greater extent ($p<0.001$)

Maximum alveolar pressure was recorded over the full inspiratory capacity range. With curarization, the pressure was reduced but lung volume seemed to be variably affected. In subjects 1 and 2, the maximum pressure-volume curve was shifted from the control in a parallel fashion during submaximal neuromuscular block. Figure 22 illustrates this for one subject. Subjects 3,4 and 5 were able to preserve inspiratory capacity to a greater extent than the maximum

alveolar pressure. The curve representing curarization has the appearance typified by subject 3 and is shown in Figure 23 where it approaches the control points with increasing lung volume.

The static passive mechanical properties of the respiratory system are summarized in Table 3. These values were determined from graphs of the pressure-volume relationships of the total respiratory system, and its components, drawn for each subject. Typical graphs are shown in Figures 24-26. When considered as a group, there were no changes in compliance, nor its reciprocal elastance, for the total respiratory system or the chest wall. Lung compliance was reduced from 0.27 to 0.24 l/cm H20 ($p<0.05$). For each subject, several measurements were made for each characteristic and in this way some individual alterations with curare were apparent on visual inspection. Only in subjects 1, 2, and 3 did lung compliance seem to be significantly reduced. Compliance of the respiratory system seemed to be decreased in subject 2 but in subject 4 it was increased. Chest wall compliance appeared to increase in subjects 4 and 5.

Also included in Table 3 are the elastance values for the total respiratory system based on the sum of the component elastances. In most cases there is good agreement between these and those determined from the whole system pressure-volume relationship.

Table 4 lists the esophageal pressure at different

lung volumes just before a static alveolar pressure was produced. There was a significant change in pressure during curarization only at the inspiratory capacity level ($p<0.001$), being reduced to 58% of control. The numerous measurements at the end expiratory position in each subject permitted the detection of subtle alterations in esophageal pressure. All showed changes, the value being less negative in 4 subjects ($p<0.001$) and more negative in subject 2 ($p<0.001$). Consequently, with the possibility that the functional residual capacity had changed, the change in esophageal pressure over the inspired volume was determined rather than simply the absolute pressure. The comparison of the two conditions is shown in Table 5. The overall conclusion remains the same however. Only at the inspiratory capacity was there any significant alteration.

To assess the effect of curare on inspiratory muscle activation, brief static inspiratory pressures of varied intensity were produced by each subject. The following description is based on Figures 27-30 to the extent that they are representative of general observations. Figure 27 has two panels showing the EMG response at the end expiratory position (denoted by symbol E) and at the inspiratory capacity (denoted by T for total lung capacity) in panel a, and those at lung volumes 1 and 2 1 (1,2) above the end expiratory position in panel b. On the abscissa, esophageal pressure has been used in preference here to respiratory

muscle pressure. Firstly, there was no consistent change in the compliance of the chest wall. Secondly, esophageal pressure is a direct reflection of the expanding force exerted on the lungs. The symbols, e, t, o, *, refer to the curare condition of E, T, 1, 2, respectively in Figures 27-30. Four aspects are noteworthy.

(1) In subject 2 shown in Figure 27a, several maximum inspiratory efforts performed at the end expiratory position (E) produced a mean maximum EMG level of 130uV. With curarization, this was reduced to 75 uV (symbol e) which was associated with a mean maximum esophageal pressure of 57 cm H2O. At inspiratory capacity, EMG was reduced from 185 (T) to 82 uV (t). In panel b, the maximum EMG was also reduced at 1 and 2 l lung volume above the end expiratory position. In 77 of the total 80 comparisons (5 subjects, 4 muscles, 4 lung volumes), the maximum EMG was decreased with curare ($p<0.001$). The mean reduction over all subjects, lung volumes, and muscles was to 41% of the control level. This will be expanded upon below.

(2) Inspiratory efforts of varied intensity were selected in order to examine the relationship between pressure and EMG. As was observed during the control series, the diaphragm EMG with submaximal neuromuscular block increased reasonably linearly with increases in pressure. In fact during curarization, the EMG of all the muscles retained their orderly increasing pattern as pressure

changed. In some cases of the extra-diaphragmatic muscles, the augmentation of the EMG developed curvilinearly, e.g. the sternomastoid of subject 5 in Figure 28 had a shallow slope over low levels of pressure which became more steep with further increments in pressure.

(3) Again similar to that seen in the control condition, lung volume had a potentiating effect on the EMG response to pressure during curarization. This is evident in Figures 27 and 28 by comparing the slope of the EMG increase with pressure at the end expiratory position with those at 1 and 2 l of greater lung volume. The greater the volume, the greater the rectified EMG for a given change in pressure.

(4) In 39 of 60 comparisons (5 subjects, 4 muscles, 3 lung volumes), the EMG during curarization was shifted to the left compared to the control data points. In Figure 27, a pressure of 45 cm H_2O at the end expiratory position evoked 37 uV of rectified EMG from the diaphragm before curare. During submaximal paralysis, that quantity of EMG was recorded at a pressure of only 26 cm H_2O. Alternatively, for a pressure of 45 cm H_2O with curare, the diaphragm produced 65 uV of EMG. Panel b of Figure 27 shows a similar displacement to occur at greater lung volumes. In 18 comparisons there were no observable shifts in the EMG response to pressure, while in 3, the displacement occurred to the right. Overall comparisons at two semi-arbitrarily

selected pressures, (i) at the pressure equivalent to the maximum passive recoil of the lung during neuromuscular block with the mean value being approximately 17 cm H2O, and (ii) at 30 cm H2O, showed the curare EMG levels to be significantly greater than the control measurements ($t=-3.74$, $p<0.001$; $t=-14.28$, $p<0.001$). Figures 29 and 30 are additional examples in other subjects of the effect of curare.

The observation introduced above that the maximum EMG is reduced with curare is further explored in Figures 31-35, one graph for each subject. These show on the ordinate, the EMG produced with maximal efforts during curarization expressed as a percentage of the control value. The abscissa is a category scale grouped according to the lung volumes at which the manoeuvres were performed and then subdivided into the 4 muscles: diaphragm (symbol D), intercostal (I), scalenes (S), and sternomastoid (N). Also included is the change in maximal muscle pressure (P). At the right of each graph is the mean percentage value and standard error of the mean for each muscle curve calculated over all lung volumes. To the extreme right is the mean change and standard deviation of all four muscles combined.

In all 5 subjects, the Pmus curve is situated within or very close to the EMG values suggesting similar levels of impairment. Although the mean values for each muscle are shown, we hesitate to attach any real significance to them in view of the large standard errors. For this reason, the

EMG at the different lung volumes is illustrated. In subject 1, the diaphragm appears to be able to produce more EMG than the other muscles only at e.e.p. and 11 above this position. The intercostal/accessory muscle decrements are similar and constant over the 4 lung volumes. The diaphragm EMG in subject 2 is only slightly greater than the other muscles except for a single intercostal value at e.e.p.+21. There is a wide range of EMG reductions in subject 3 but the diaphragm curve is located in the upper portion of the graph. At e.e.p.+21 and at inspiratory capacity for subject 4, diaphragm EMG is less affected than the other muscles. At the lower lung volumes, there is no difference. Over all lung positions in subject 5, the EMG decrements in all the muscles are superimposed. Analysis of variance and post-hoc treatment of these data (Tukey A) indicated that the scalenes just showed a significantly greater decrement in the maximum EMG than the diaphragm during partial curarization ($p<0.05$) while the intercostals and sternomastoid muscles did not.

CHAPTER V

DISCUSSION

V.A. DISCUSSION OF CONTROL STUDY OF RESPIRATORY MUSCLES

To assess the degree of activation of the inspiratory muscles during curarization, we must first know the pattern of contraction under control conditions. Since valid EMG comparisons can only be made if the electrodes have remained at the same recording site, it would have produced an unduly prolonged experiment for the subject if control and curare measurements were performed in the same experiment. Therefore, the pre-curare control measurements were condensed, but preceded by several days by a full control investigation.

Although the work of Campbell [44] appears to be the only report describing an investigation similar to the one presented here, no quantification of the electromyograms was made. We recorded the EMG from the diaphragm, the intercostals, the scalenes, and the sternomastoid on the basis that they are the primary muscles responsible for inspiration [46]. Several limitations exist with respect to our methods of measurement.

V.A.a. Limitations of methods

1) Single muscle site recording may not be representative of the whole muscle. The crural diaphragm EMG was recorded with an esophageal electrode. We know that the crural and costal portions have different embryological origins, with separate innervation patterns. Recently, DeTroyer and Sigrist [71] showed that the two parts can have different actions on the chest wall, and therefore it is possible that the behaviour of one part may affect the other. Other methods available are also site specific. Transthoracic recordings of the diaphragm with surface electrodes may be contaminated with intercostal EMG. This problem has been discussed by Campbell [44]. Concentric needle electrodes as used by Taylor [253] can be uncomfortable with most respiratory efforts, except for those of a more mild nature. Fine wire electrodes, although more tolerable, record from a very limited area. The esophageal technique measures diaphragm electrical activity across the esophageal wall therefore some filtering of the compound action potentials is likely to occur. A gastric balloon can be attached to the esophageal catheter so that the electrode moves in concert with the diaphragm [116]. We did not follow this procedure because static inspiratory efforts require that noseclips be used. This almost eliminated catheter motion. Furthermore, the floor of the nasal cavity, particularly at

the anterior portion became sensitized to the movement of the catheter over extended periods of time. To avoid this, the catheter was taped to the tip of the nose. This fastening performed at the subject's inspiratory capacity meant that the electrodes would have been in their most caudal position. Therefore, the electrode was further from the diaphragm when the end-expiratory position was assumed, and potentially the EMG could be reduced. With an audio amplifier and loudspeaker however, even the weakest diaphragm contractions could be detected suggesting minimal loss of our signal. (It is possible that the large gastric balloon floated in the stomach and pressed against the cardia sphincter. This would tend to keep the catheter electrodes close to the diaphragm.)

2) It is possible that the parasternal intercostal surface site does not produce a true intercostal signal. Several layers of tissue exist in the area of these small fibres, the pectoralis major being the most notable. No phasic activity with quiet respiration was heard in this region as is possible with needle electrodes, so some threshold level of EMG was needed before recruitment could be detected. The pectoralis presented little problem since the electrodes were placed as medially as possible in relation to it, and conscious activation of the muscle produced EMG several orders of magnitude larger than the intercostal signal.

3) The thin platysma, extending in a collar fashion from the mandible to the chest, could contaminate recordings from the scalenes, and sternomastoid. Similarly, the proximity of the sternomastoid may cause it to distort the scalenes' EMG measured. In order to reduce the interference, both in the case of the platysma and the sternomastoid, the subjects learned to perform the manoeuvres without grimacing or pulling the head forward. In practice, these really only require attention during the more strenuous efforts. Proper placement of the scalenes electrodes was confirmed when during a slow deep inspiration that muscle was recruited before the sternomastoid, a larger more superficial muscle.

V.A.b. EMG analysis of control data

In this investigation the electromyograms of the four primary inspiratory muscles were studied within the static respiratory pressure-volume map, that is, at different pressures and lung volumes. The lung volumes were restricted to the inspiratory reserve volume. Such a diagram is a useful representation of the mechanical reserve of the respiratory musculature. Each breath utilizes some proportion of this total potential for work and it may be viewed in relation to the pressure and volume limits of the respiratory system. This study explores the

electromyographical correlates of the map aiming to determine the extent of activation of the diaphragm, intercostal, scalene and sternomastoid muscles.

Due to the nature of the data presented here, traditional statistical indices do not accurately demonstrate the interaction between pressure, EMG, and lung volume for the four muscles. Therefore, as part of an overall analysis of the various influences, schematic illustrations have been made to represent the average responses of the five subjects. There are distinct differences between the behaviour of the diaphragm and those of the intercostals, scalenes and sternomastoids. For the latter group, the term of Grimby and associates [120], intercostal/accessory muscles, is an appropriate collective description. In Figures 36a-d, the EMG is depicted in response to changes in total respiratory muscle pressure over five inspiratory lung volumes (end expiratory position = functional residual capacity, one, two and three litres above e.e.p., and at inspiratory capacity). The rationale for this arrangement rather than transdiaphragmatic pressure for the diaphragm is that the concern is primarily on the ability to inflate the lungs. To this end, pleural pressure (esophageal pressure) must become more negative to overcome the elastic resistance due to lung and chest wall recoil. Increases in abdominal pressure may assist the diaphragm but it is not a prerequisite for inflation. For any curve shown, a reasonable variation for the

EMG magnitude would be approximately 10% in either direction.

The two distinguishing features in Figure 36a are the activation of the diaphragm at very low levels of pressure, and the linear increases in EMG as the pressure is changed. Consider first the bottom most relationship where the chest wall is at its e.e.p. and lung recoil inward is exactly opposed by chest wall recoil outward to establish the functional residual capacity. For the slightest decrease in alveolar pressure the diaphragm is immediately recruited. At any particular lung volume, the changes in muscle length with each additional pressure increment are probably not significant. (Decompressing alveolar gas by 100 cm H20 would be similar to increasing thoracic volume at e.e.p. by approximately 0.25 1.) Therefore the constant increase in EMG over pressure strongly implicates increasing diaphragm participation.

At e.e.p., the intercostal/accessory muscles (Figures 36b-d) were minimally involved until moderate pressures were produced. This could be associated with the necessity for some pressure threshold to initiate their recruitment, or failure of the recording techniques to detect minor levels of electrical activation. With increases in static inspiratory pressure, the EMG changed in a curvilinear manner. Linear responses in the rectified electromyogram with force would have been expected from what is known of

limb muscles [169] and the diaphragm, [117] however Raper and associates [219] also observed curvilinear EMG changes in the scalenes and sternomastoid.

V.A.c. EMG and force

The coupling between mechanical and electrical events in muscle was demonstrated many years ago. Liddel and Sherrington [164] and Adrian and Bronk [1] studying individual motor unit action potentials, observed that contraction strength could be augmented by motor unit recruitment and increased firing frequency respectively. The particular contribution to the force produced by each of these methods is a topic of active debate [50,188,189,194,251,252]. However it is unlikely that either of these patterns could exist without involvement of the other given the many factors affecting motor unit participation such as motor unit type, variation of the firing threshold over time, extent of any previous motor unit activation, and direction and rate of force development [42].

DeLuca's [61] analysis offers a useful description of the myoelectric signal. The shape of the action potential of a single muscle fibre depends on several factors. (1) The location of the recording site with respect to the direction of the depolarization of the muscle membrane,

determines whether the potential appears as a negative or positive phase. (2) The action potential amplitude is decreased, the smaller the muscle fibre diameter, the greater the distance between the contracting fibre and the electrode, and the greater the filtering properties of the electrode. (3) A long action potential is observed from a fibre with a low conduction velocity. (4) Differences in motoneurone branch and muscle fibre lengths cause slight delays in the observed onset of the potential. (5) Tissue between fibres and the electrode has a low pass filter effect on the action potential frequency spectrum.

When a single motor unit is depolarized once near an electrode, the spatial and temporal superposition of the individual fibre potentials produce a unique motor unit action potential and may consist of several phases. Its particular shape however will be modified by the arrangement of the electrodes in relation to the contracting fibres. Electrodes placed longitudinally with the fibre direction transmit the largest signal whereas a transverse alignment produces the weakest. The final recorded motor unit action potential will have undergone additional modification introduced by the presence of system instrumentation noise and filtering properties of the electrodes and the recording equipment.

Unlike the simple twitch just described, most muscle contractions require the involvement of more than one motor

unit and they are stimulated at least several times. A motor unit action potential train is produced by each unit, but the electrode will record many trains, some from units near it, and others from motor units more distant. The superposition of these trains produces the interference pattern of the electromyogram, but due to the high number of trains, it is difficult to separate the extent of motor unit recruitment from firing frequency except in less vigorous muscle contractions. The rectified electromyogram quantifies the total electrical activity of the muscle detectable by the electrode. Its magnitude will depend on the total area of the motor unit action potentials, and will increase if there is recruitment or an increase in firing rate. Some electrical cancellation will occur whenever synchronous potentials are of opposite phase.

The linear relation between isometric muscle force and the rectified electromyogram has been a frequent observation and would be expected since the size of both are determined by the same factors. Indeed, in a situation of single contractions where the number of active fibres was steadily decreased by means of a slow infusion of curare, the area enclosed by the action potential recorded with intramuscular electrodes varied linearly with twitch tension [23]. In contrast, the amplitude of that potential changed in curvilinear manner, showing little alteration with the higher tensions.

The electrical linear superposition of independent units was demonstrated by Biro and Partridge [28]. They found that as more asynchronous action potentials were added, the probability distribution curve of the instantaneous EMG amplitude changed. It evolved from a curve with a high likelihood of signal cancellation and a narrow range of extreme voltage on either side to a more normal distribution, that is, a decreasing chance for zero voltage and a wider spread of possible amplitudes. It was proposed that the variance of the voltage probability distribution could be a reliable indicator of the excitation level of the muscle. The integrated EMG in contrast grew logarithmically with the number of action potentials rather than linearly. This was consistent with simulation studies [195,212].

Subsequent analysis was partly in concurrence with this theory. Whereas Biro and Partridge [28] suggested that recruitment and firing rate are likely to have similar effects on the EMG, Milner-Brown and Stein [190] calculated that only the addition of motor units could produce the logarithmic pattern. The EMG changes induced by excitation frequency were more directly proportional. When the surface EMG amplitude was computed assuming a linear summation of the "amplitude" of the signals contributed by single motor units, it increased linearly with muscle force if the effects of both recruitment and rate coding were considered. However in the condition of linear summation of the

"variances" of these same signals, as force increased, the rectified surface EMG changed logarithmically. These results suggest that alinear changes in the electromyogram rather than linear, are more likely responses to progressive alterations in motoneurone discharge pattern.

Another factor which complicates the relationship between force and EMG is one of muscle fibre inhomogeneity. The above analyses have assumed that the motor units had similar physiological properties, their muscle fibres were equally distributed throughout the muscle area under study, and that recruitment was not limited to particular locations within that muscle. There is evidence in animal muscle that fibres are not of the same size, although in man this is less certain [39]. But to a certain extent this is corrected for since both action potential amplitude and force are determined by the cross-sectional area of the muscle fibre [122]. If there was more recruitment or firing frequency increases in muscle regions close to the electrode, the electromyogram would grow at a faster rate than force. This may be less of a problem in small muscles such as the first dorsal interosseus [190]. In man, not all motor units are histochemically alike [142] and their recruitment appears to be determined by their size and muscle fibre type [204,267]. Generally, the fast contracting, high-threshold motor units are employed only when more forceful efforts are required. These motor units have large

action potentials [38,156] and therefore would produce more EMG for a unit increase in force, particularly if they are located in more superficial regions of muscle such as occurs in the biceps brachii [50].

Many of these factors appear to explain the observations of Bigland-Ritchie and her associates [27] who investigated the force-EMG relationship of seven different human muscles. The smooth-rectified EMG increased linearly with force up to the maximal voluntary tension in the soleus, adductor pollicus, and first dorsal interosseus. These muscles are predominantly of slow twitch muscle fibre composition, and increase force mainly through increasing firing frequency. The biceps brachii, triceps brachii, and brachioradialis have a more mixed fibre type pattern and depend heavily on recruitment. In these, the EMG increased slowly provided force was less than 25 - 35% of the maximum. With greater tensions, the EMG increase was more rapid.

Although increases in excitation frequency can be expected to increase the rectified EMG rather linearly [190], the force increment may not be proportional due to the sigmoidal shape of the force-activation frequency relationship [24,41,56,215]. Motor nerve stimulation studies show that excitation at 60 Hz will generally produce complete muscle tetany. However, in these techniques all motor axons are stimulated simultaneously. Lind and Petrofsky [167] showed that during asynchronous excitation, fusion can

be achieved at 30 Hz. This means that, especially in muscles dependent on rate coding, it would be possible to record increases in the EMG while little force was added, albeit, at efforts near maximum voluntary contraction.

From all these considerations, stepwise alterations in motor unit firing pattern should produce anything but linear responses between the electromyogram and tension. Under controlled conditions however it is possible for EMG and force output to vary proportionately as a result of their common alinearities.

Unlike the diaphragm in which the EMG increased fairly linearly over the full range of pressure, the EMG of the intercostals, scalenes and sternomastoid increased at a more rapid rate once moderate efforts were produced relative to the maximum for the particular lung volume. This confirms earlier observations [219]. In addition to the many factors controlling the measured EMG just discussed, these responses could represent true increases in muscle tension which do not contribute directly to further reductions in intrathoracic pressure but may have a function related to maintaining stability of the thoracic cage. It is also possible that in the case of the scalenes and sternomastoid, changes in head position were made during the more strenuous static manoeuvres. This could increase the tension of the muscle even though instructions were given to maintain the neck relaxed. If there was a significant amount of motor

unit synchronization at the greater pressures, theoretical analysis would predict a greater increase in the EMG. The muscle tremor often associated with such efforts would be consistent with such an explanation.

V.A.d. Effects of lung volume

In Figure 36a we next consider the effects of increases in the lung volume. The circle to the left of the second most bottom curve represents the range of the diaphragm EMG produced on inflating the lungs by 1 litre and momentarily maintaining that position with an open glottis. No attempt was made to quantify the EMG during active changes in muscle length in light of possible contraction velocity effects [25]. We would expect however that the EMG would increase reasonably linearly from the origin and through each of the circles associated with successive increases in the size of the breath. As indicated earlier, at each lung volume pressure elicited proportional changes in the diaphragm EMG but for a particular Pmus to be produced at a greater inspired level, more EMG was present. The intercostal/accessory muscles responded similarly to volume changes.

Grassino and his associtates [117] who observed the same trend in the diaphragm EMG as the volume was increased, cited the work of Libet and co-workers [162] for a possible

explanation. It was suggested that the difference in the rectified EMG amplitude of maximum contraction, up to two fold, was primarily due to autogenetic inhibition of motor units. Inhibiting afferent impulses from tendon organs in a lengthened muscle results in a reduced electromyogram. Observations from two conditions in which tendon organ function would be expected to be compromised supported this proposal. The EMG from lengthened muscle was decreased to a lesser amount in patients with tabes dorsalis and in normal subjects in whom procaine was injected into the tendon region. The reduction in motor unit action potential counts with increasing muscle length for a particular level of pressure is consistent with this notion [51].

(Tendon organs are more easily excited during muscular contraction compared to that during passive stretch and when the muscle is at short lengths [246]. Tendon organs have been shown to be increasingly active in the diaphragm during inspiration [57]. Houk proposed that as monitors of force, tendon organs cooperate with muscle spindles, the informers of length, to regulate the "stiffness" of muscle (force change relative to length change) thereby reducing the effects of sudden changes in muscle load [130].)

At variance with the conclusions of Libet and his group [162] are reports indicating minimal effect of joint position on motoneurone excitability [176,227]. This becomes evident when the EMG at a particular muscle length

is considered relative to the M-wave, the electrical response evoked on maximal transcutaneous twitch stimulation of the motor nerve. The M-wave always changed in proportion to the EMG produced during maximum voluntary contraction indicating that there was a geometrical alteration between the surface recording electrode and previously monitored muscle fibres. The EMG issue is no clearer in stimulated muscles in animals [161,247]. However as McComas and associates caution, the absence of less EMG in a lengthened muscles does not necessarily indicate the absence of the autogenetic inhibition. It is possible that central afferent excitation is simply more prominent.

If the Golgi tendon organs have a significant involvement in the amount of EMG produced, it is doubtful that this mechanism could explain all of the several fold difference in respiratory muscle EMG for a given moderate pressure when lung volume is changed. It is important to consider the implications of this observation. As an example consider Figure 36. In order to maximally inflate the lungs, the respiratory muscles were required to produce a total muscle pressure of approximately 40 cm H20. For the moment, it will be assumed that the respiratory muscles can be fully or near fully activated, that is, involve all motor units at tetanic frequency. In order to achieve the same muscle pressure at the e.e.p., the rectified EMG values of the diaphragm, intercostal, scalenes and sternomastoid were

22, 5, 20, and 12% respectively of the level at inspiratory capacity. At the e.e.p., any muscle effort is immediately expressed as a change in pleural pressure if the airway is closed. To arrive at TLC, the elastic recoil of the chest wall must first have been overcome before any deformation occurred to the lung. If pressure was expressed solely as esophageal pressure, the EMG would be underestimated at e.e.p. and overestimated at TLC. Account is made of this difference however, by expressing the EMG relative to total muscle pressure. The family of curves is therefore brought slightly closer together (see Figure 15 vs Figure 16). Nevertheless, there is still less electrical activation of the muscle fibres at lower lung volumes and we next consider various aspects of this observation.

As noted earlier, Grassino and his co-workers [117] indicated that autogenetic inhibition of motor units might explain the reduced EMG. However, if inhibition decreases the EMG, why is pressure not also reduced? Inactivation of motor units at long muscle lengths should prevent muscle force from being developed. In contrast, our results show that more force is being produced. We can only offer that perhaps the reflex inhibition acts to restrict the extent of rate coding in motor units rather than recruitment. Then tetanic frequency might be prevented which would reduce the EMG as was shown earlier, but still allow effective temporal summation so that high levels of muscle tension could be

developed. For such an explanation to be accepted however, assumes that tetanic excitation frequency can occur in some motor units at levels of respiratory muscle pressure which are in the low to moderate range. This would be in contrast to the most popular concept that recruitment is primarily responsible for increases in force over low grades of tension [106,137,188,189,194].

Traditionally, it has been felt that respiratory muscles, like other skeletal muscles, follow length-tension (and force-velocity) relationships [79]. Since muscle shortening reduces the overlap between the contractile filaments [114], and/or inhibits the inward spread of depolarization by transverse tubule distortion [215], it may be argued that for a given level of electrical activation, a longer muscle should produce more tension. This has been illustrated by experiments where constant maximal phrenic nerve stimulation results in decreasing force as the diaphragm is shortened [149,177,209]. As a consequence, for a constant level of tension, a lengthened muscle should require less excitation as evident either by the electromyogram [117,118,219,236] or phrenic nerve activity [88,90].

Grassino and his associates [117] have clearly shown that even though lung volume is held constant, the diaphragm can be lengthened or shortened and decrease or increase the EMG respectively. We have not used magnetometers nor measured anterior-posterior abdominal diameter, but lung volume

is no less meaningful as an indicator of diaphragm length. Each subject was allowed to select his own chest wall configuration during inspiration. Moreover, even if abdominal anterior-posterior diameter was kept constant, the diaphragm assists expansion of the thorax by lifting the lateral segments of the rib cage and therefore it must shorten to a certain extent [79,233].

For practical purposes, most muscles rarely operate over the entire length-tension curve as depicted in the traditional diagram where length can be so short that no force is produced [247]. Stephens and his group [247] have identified the full in-situ tetanic tension curve as occurring over approximately 38 mm of muscle length change in a cat gastrocnemius 140 mm long. During natural movements however, the change in muscle length was only 20 mm and with simple locomotion, electrical activity was present in only a range of 15 mm. Most importantly, the peak of the tension curve occurred within the lengths naturally used. These observations essentially confirm those of Grillner [119] who also showed that this movement range can make use of peak muscle "stiffness".

There are complicating factors to be noted though. (1) The optimum length for tetanus may not be the same as for the muscle twitch [161]. (2) Selective activation of only one type of motor unit may not have the same effect as that of the parent muscle [247]. (3) Particular frequencies

of muscle excitation re-position the peak tension and the actual tensions on the descending portion of the length-tension curve [176,215,227]. (4) Muscle fibre length may not necessarily be reflected by muscle length because pinnation can alter the relative degree of stretch [200] and sarcomeres in the middle portion of a stretched muscle fibre are usually longer than those nearer to the ends [135].

Such information is more limited with respect to the respiratory muscles even though Rahn and his associates [216] suggested length-tension relationships to explain the maximal pressure-volume diagram of the chest wall as early as 1946. The studies of Kim and associates [149] indicate that in the dog, the diaphragm must shorten to 37%, corresponding to a lung volume of 1200 ml above FRC of its in-situ length, before it can no longer develop tension. Maximal tension is achieved at 125% when lung volume is 400 ml below FRC. At FRC, the negative pleural pressure improves the effectiveness of the diaphragm by lengthening it by 16% but by increasing the volume by an additional 600 ml only 17% of the maximal tension can then be produced. Thus the mechanical reserve of the muscle is greatly reduced at that intermediate level of inflation. The proportion of the total force needed for a breath of that size was not measured though.

These measurements of Kim and associates corroborates with the calculations of Fenn [94]. From

radiographic photographs, he first estimated the length of diaphragmatic fibres at residual volume to be 12.5 cm. (Recent autopsy studies of Arora and Rochester [15] show that in average healthy males, diaphragm muscle fibres are 10-11 cm long.) Following deep inspiration they shortened by approximately 48%. The diaphragm differs from skeletal muscle therefore, in that it shortens to a greater extent in vivo and is able to develop tension over a larger portion of its potential length change. Detailed mechanical comparisons among muscles however must consider that within a muscle, and from one muscle to the next, not all fibres need run in the same direction, and if they do, the direction of shortening may not act in parallel to the target load.

Estimates of intercostal changes will be even more variable since their behaviour throughout the rib cage is not the same [44,253]. Fenn [94] reports shortening of 12-25%. A figure used to explain Hamberger's theory of intercostal action on the ribs [5] would have the external intercostals shortening by 5% on inspiration. Raper and his coworkers [219] using calipers, measured the scalenus medius muscle to decrease in length by 5% during the vital capacity test. Although the length-tension relationship of muscle is accepted as one of the foundations of respiratory mechanics, there is very little concrete evidence indicating the extent of its importance in man except perhaps for the diaphragm.

The analysis of Mead and Agostoni [180] may be used

to put the issue of the length-tension relationship in its proper respiratory perspective. When the maximal muscle pressure and air flow are graphed in relation to lung volume, we have the total mechanical potential available. The large reserve inherent in the respiratory system is obvious when those values obtained during rest and exercise are included in the diagram. "At rest some 12% of the potential volume change, 6% of the potential flow, and 3% of the potential pressure are used. During heavy exercise the corresponding values are 50, 50, and 15%" [180] (pg 423). Since only 15% of maximal muscle pressure is used even during high intensity physical activity, clearly one would rarely encroach upon the limits set down by length-tension interactions. If it was, fatigue would follow with the rapidity of onset determined by the magnitude of the respiratory load [21,225].

V.A.e. Recruitment of respiratory muscles

To the extent that diaphragmatic EMG is correlated to the integrated phrenic neurogram [172] and might be used as an index of neurogenic drive, the pressure-EMG relationships described here also illustrate a reserve of electrical activation. On the average, for an inspiration of 1 l from e.e.p., only 5, 0.1, 1, and 0.1% of the maximal EMG at inspiratory capacity was required respectively for the

diaphragm, and the intercostal, scalene and sternomastoid muscles (Figure 37a). Furthermore, to develop a total muscle pressure at this lung volume equivalent to that produced at inspiratory capacity, the EMG levels are 31, 9, 36, and 23% respectively (Figure 37b), still far removed from the limits of the system. It would be most efficient for respiratory muscle pressure to be developed at as low a lung volume as possible where inspiratory muscle length is long. Druz and Sharp [81] suggested that neuromuscular efficiency may be described by the ratio of Pdi/Edi. During tidal breathing, they found that the diaphragm was more activated in the upright position. When a given Pdi was produced in that posture compared to the supine position, efficiency was only one-third as great. From our observations, the EMG/Pmus ratio, i.e. slope on the linear portion of the graphs, is least at the e.e.p.. The increase in the EMG for an increase in static alveolar pressure becomes progressively greater as the starting lung volume is elevated. Presumably, as lung volume increases, the muscle fibres must shorten thereby reducing the number of potential sites for interaction between the contractile proteins. To achieve the same negative alveolar pressure, more muscle fibres must then be activated. Just as most skeletal muscles exert much of their tensions over their most effective part of the length-tension curve, the diaphragm and accessory muscles are returned to longer lengths after an inspiration by the

elastic recoil of the respiratory system. This is likely to be near the optimum position for pressure development with minimal requirements for neural input. A lower FRC would need tonic participation of the expiratory muscles.

Various methods have been used to assess the relative contributions of the different respiratory muscles to the act of breathing. Those include circumferential measurements [6,8], circumferential and radiological median-sagittal displacement [260], anterior-posterior displacement by magnetometry [111,152,239], electromography [44], partitional plethysmography [22], and ballistic techniques [261]. The latter two methods only provided information from supine postures.

Agostoni [10] has summarized that there is relatively good agreement among the estimates for the volume contributed by the various parts of the respiratory system in the upright position. In the typical vital capacity manoeuvre, the rib cage accounts for approximately one third while the diaphragm is responsible for the rest. Of that remainder, one-half is evident as abdominal displacement. Vertical movement of the rib cage caused by lifting by the diaphragm constitutes the other half.

Campbell [44] pointed out that a complete functional description of a potential respiratory muscle would include its mechanical action, its respiratory function, and the circumstances under which it contracts. Electromyography

alone cannot fulfill all these roles but is useful in characterizing the latter. His premise was that if a change in EMG correlated with the intensity of the effort, it strongly suggested a direct contribution by that muscle. With quiet breathing, he could detect EMG only in the lower intercostal spaces. As the tidal volume was gradually increased, the upper intercostals, the scalenes and then the sternomastoid were recruited. Static inspiratory pressures evoked EMG in the neck muscles when approximately -30 cm H2O was reached. To activate the upper intercostals, pressure had to be increased to approximately -60 cm H2O.

Based on Campbell's reasoning, the EMG responses observed here have been impressive in terms of their orderly increase with pressure and lung volume. Although this pattern has probably been speculated on numerous occasions, this could not have been verified until the techniques described in this report had been used. Utilization of graded static inspiratory efforts allows a clearer discrimination of the circumstances of contraction of a muscle. For example, referring to Figure 36, the complete range of EMG levels is produced by only 45 (45-0=45) and 30 (45-15=30) cm H2O of muscle pressure for the diaphragm and intercostal/accessory muscle respectively if lung volume is the only independent variable. As such, static manoeuvres elicit more gradual changes in the EMG and illustrate the interaction produced by alterations in the muscle length.

By definition, static refers to that condition which allows study of the elastic component of impedance to motion, with elimination of flow resistive and inertial factors. It was assumed that it also represents a condition of constant lung volume and therefore constant muscle length. This cannot be completely so. For a negative alveolar pressure to be produced, with an occluded airway, there must be expansion of the chest wall. This can only come about from muscle shortening. A pressure of -100 cm H20 produced at an FRC of 2500 ml would be equivalent to displacing the chest wall by an amount achieving a total lung volume of 2770 ml under ambient pressure conditions. At 3 litres above FRC, -30 cm H20 would be equivalent to adding 165 ml to the lung volume. These "equivalent" volume changes are similar to the normal variations seen in FRC [128] and probably have only a minor effect on altering muscle mechanics.

It must be realized however that the "equivalent" volume need not be equally distributed throughout the chest. Deformation of the rib cage occurs which is different from that seen on inspiration. Static inspiratory efforts performed at e.e.p. or residual volume cause the dorsal-ventral diameter to decrease and the lateral diameter to increase. When breathing is performed through a resistance, the dorsal-ventral diameter change lags behind the lateral diameter [8]. This suggested that the respiratory muscles acted on the lateral portions and that this movement, along with

the pressure across the chest wall, influenced motion of the more passive anterior part. Any deformation would increase the calculated work of breathing over that determined from the pressure-volume diagram. In an extension of this work, Saunders and his group [233], first confirmed the increasing ellipsoidal cross-sectional shape of the rib cage at low or modest lung volumes observed by Agostoni and Mognoni [8]. When static inspiratory efforts were performed above 50% of inspiratory capacity, both anterior-posterior and lateral diameters of the rib cage increased. Both diameters also increased at FRC if intercostal-accessory muscle contraction was emphasized, producing minimal change in abdominal pressure. Prominent diaphragmatic activity, as indicated by a high transdiaphragmatic pressure, again decreased the rib cage anterior-posterior diameter. Finally, independently of the lung volume, static inspiratory efforts performed with a small anterior-posterior abdominal diameter made the rib cage cross-section more ellipsoidal and a large abdominal anterior-posterior diameter, associated with the diaphragm in a more caudal position, made the rib cage more circular. In general therefore, a chest wall configuration in which the diaphragm was shortened, that is increased lung volume or lengthened anterior-posterior abdominal diameter, caused the rib cage to become more circular, provided that the abdominal pressure changed minimally. An ellipsoidal shape was produced, if the diaphragm was long or significant

abdominal pressure was generated. These results indicate that transmural pressure could not contribute significantly to the rib cage deformation and agree with Agostoni and Mognoni that in some instances intercostal/accessory muscles appear to be lengthening, as when the anterior-posterior diameter decreases, when they would be expected to shorten.

Sampson and DeTroyer [228] have recently shown that not all individuals distort the rib cage. In these cases significant EMG can be recorded from intercostal muscles which implies a stiffer rib cage. Where rib cage deformation occurred, there was no EMG. Our observations concur with those of Sampson and DeTroyer. Two of five subjects (subjects 1 and 3) showed little parasternal intercostal EMG in response to static inspiratory efforts when performed at e.e.p. and even at 1 l above this volume. In the other three, the EMG increased linearly with pressure beginning with very low efforts. Oddly though, in this latter group, diaphragm EMG was also very prominent when it might have been expected to be less considering the activation level of the intercostals.

From the hypothesis of Goldman and Mead [111] regarding the prominence of the diaphragm in breathing and the apparent motion of the rib cage along its passive pressure-volume curve, the actual role of the intercostals is questioned. A respiratory function for the intercostals is an undisputed fact [44,47,59,253] but Sampson and

DeTroyer [228] reported that there was little voluntary control over their participation even when suppression of the intercostals was attempted by "diaphragmatic breathing" and auditory feedback of their EMG. In addition we show that intercostal electrical activity is closely linked to inspiratory pressure and lung volume. According to Viljanen [258], the intercostals are "programmed" before the breath. For inspirations of similar size, action potential count from the intercostals was variable but once the muscle was recruited, the counts increased linearly throughout the breath.

Earlier, lung volume increases were described as partitioned between diaphragm descent and rib cage expansion but Konno and Mead [152] have shown that most lung volumes can be achieved by a number of different chest wall configurations. From measurements at FRC at least, voluntary distortion of the chest wall causes minimal disturbance of the regional lung volume [115]. At the inspiratory capacity however, there was little choice for the shape the chest wall could assume. Does this suggest maximal activation of all muscles? If so, it would allow each muscle to be described with respect to some reference of activity. Campbell [44] addressed this issue concluding that antagonistic muscles and/or reflex inhibition of the agonists prevented any further increase in volume over the measured inspiratory capacity. The possibility of glottic closure was dismissed

by Mead and his associates [179]. At the inspiratory capacity level, the respiratory musculature must overcome the elastic recoil of the lung and chest wall so it has not reached a point of zero tension. Indeed, Pmus may be as high as 30-50% of the maximal pressure recorded at e.e.p..

There appear to be no reports to determine whether the respiratory muscles can voluntarily be maximally activated. Some peripheral skeletal muscles at least, ankle dorsi flexors and ankle plantar flexors, seem to be fully and near fully activated respectively as indicated by the inability of an interpolated twitch to significantly augment torque [20]. The adductor pollicis can also be maximally activated voluntarily [183]. Mognoni and his co-workers [192] have approached this problem by measuring the speed with which esophageal pressure decreases on tetanic stimulation of the phrenic nerves. Since the time course was similar to that found in other skeletal muscles, no extra mechanical limitation should prevent maximal excitation of the diaphragm. It is believed therefore that our measurements of EMG and muscle pressure are maximal.

Two aspects are noteworthy in interpreting the maximal transdiaphragmatic pressure. (1) Since our subjects were uninstructed as to the manner in which the static inspiratory manoeuvres were to be performed, all EMG and pressure responses are those of spontaneous efforts. Any combination of muscle activation and chest wall

configuration was available and a given esophageal pressure could be associated with an increased, decreased or constant abdominal pressure. As DeTroyer and Estenne [70] and Gibson and his group [108] have pointed out, maximal Pdi can be increased in healthy individuals easily by coaching on the production of abdominal pressure. Occasionally, the spontaneous effort produced the greater pressure in their studies. Some of our individual data points, particularly those of maximal and near maximal transdiaphragmatic pressure, support the variability of abdominal pressure. For the most part though, we are satisfied that the efforts were performed in a consistent manner in each subject.

(2) Voluntary tests of volume and pressure are only indicative of the functional reserve of the respiratory musculature. Since there is evidence in cats that the autonomic control of the muscles descends the spinal cord in different tracts than those used for voluntary activation [202], vital capacity and maximal inspiratory pressure tests could have only limited relevance to respiratory regulation or neuromuscular integrity. Clinical cases have been cited which demonstrate that either the voluntary or the involuntary control can be impaired while the other system remains functional [214]. According to animal studies, the phrenic is the only motor nerve for the diaphragm [229], although the three phrenic roots innervate different parts of the muscle [71].

Much of this discussion has been based on mechanical similarities between skeletal muscles and the respiratory muscles. As for their pattern of participation, respiratory muscles differ from skeletal muscles. In the general equation of motion, muscular force is required to balance the forces due to inertia, friction and elasticity. Inertia is the primary obstacle in rhythmical movement of a limb. A flexor muscle contracts miometrically initially. When maximal velocity is attained, the extensors begin to contract pliometrically and eventually stop the limb's movement. Then the pattern may be repeated in the opposite direction with the extensors behaving as agonists. By comparison, respiratory muscles deal with elastic and frictional resistance [94], the former in a normal breath being generally 5-fold greater in magnitude. (1) Miometric contraction on the part of the inspiratory musculature continues until the appropriate volume is reached. (2) The greater the size of the breath, the greater is the elastic recoil. (3) The muscle shortening imposes a slight mechanical disadvantage. As a result of these differences, neuronal drive to muscle must increase over the course of inspiration. Analyses based on constant EMG [117] therefore have limited application.

The progression of EMG with increases in inspired volume may be followed by joining the left most points of each curve in Figures 36a-d resulting in Figure 37a. For

the diaphragm the joining line passes through the origin, because in each subject the slightest inspiration elicited EMG. The larger the breath, the greater was the EMG as is already known [3,106,143,213]. Gesell and his co-workers [106] explained the increase in diaphragmatic EMG as being due to an increase in the excitation frequency of those units firing early in the breath and the recruitment of more and more units as the inspiration continues. By the end of the breath, the excitation rate of the early units was more rapid than that of the later ones and presumably would be close to their tetanic tension. The recent findings of DeLuca and his associates [62,63], who studied isometric contractions in skeletal muscle with force varying intensities, support Gesell's observation. Not only does the intensity of contraction increase to overcome greater elastic recoil with volume, but the diaphragm also shortens. Presumably this explains the difference in the level of EMG for the same pressure at different lung volumes as discussed earlier. The issue of diaphragm curvature is less important than previously considered [177] according to recent investigations [35,149]. If the EMG measured at inspiratory capacity represents a maximal level of diaphragm activation, and inspiring 3 l from e.e.p. only produces EMG of approximately 50% of that amount, it seems unlikely that the diaphragm would reach total recruitment before being very close to complete lung inflation. The implication of this

is that the diaphragm is active and capable of producing pressure in every phase of inspiration regardless of breath size.

With respect to the intercostal/accessory muscles depicted in Figures 36b-d, when low inspiratory pressures were produced at low lung volumes, there was little EMG. Moderate pressures generally recruited the scalenes before intercostal and sternomastoid activity could be detected. Continued increases in alveolar pressure then typically elicited curvilinear responses in the EMG. During an inspiration to 1 l above e.e.p. the intercostal/accessory muscles remained silent but were more readily activated with added static pressures than at the e.e.p. lung volume. This suggests a recruitment threshold shift along the pressure axis toward the origin. The threshold was advanced further when the inspiratory pressures were produced at 2 l above e.e.p. and there was an increase in the slope of the EMG response over the pressure range. Approximately 5% of the maximum scalene EMG was utilized to attain this lung volume. All muscles participated in inspiring to 3 l. In relation to their level at full inspiration, the mean intercostal, scalene and sternomastoid EMG values were 16, 32 and 11% respectively.

In virtually every inspiration and static pressure tested, the diaphragm was activated to a greater extent in relation to its maximum EMG than the other muscles. This is

consistent with the first quantitative evaluation of the diaphragm made by Wade [260] who, by combining spirometry, circumferential assessment and radiology, calculated it to contribute at least one half to a normal quiet breath. Many subsequent investigations have confirmed the diaphragm's mechanical action [58,193,230,231], claiming that it is the major inspiratory muscle.

V.B. DISCUSSION OF CURARE STUDY

V.B.a. Effect of curare on skeletal muscle EMG and mechanics

Neuromuscular junction. Curare has traditionally been regarded to inhibit muscle depolarization by reversibly attaching to acetylcholine sensitive receptors on the post-synaptic membrane [113]. This was based on the observation in in-vitro frog muscle preparations that curare follows chemical reaction kinetics typical of classical competitive inhibition [140]. Furthermore, the normally permanent binding of alpha-bungarotoxin to acetylcholine receptors is delayed by curare [185]. As Magleby and associates [175] summarize however, additional actions by curare are being recognized which include interference with the pre-synaptic release of acetylcholine, depletion of acetylcholine stores during repetitive stimulation, and possible blockage of ionic channels at the end-plate surface. Irrespective of the mechanism, the result is a reduction in the size of miniature end-plate potentials [92] which prevents the end-plate from reaching the depolarization threshold [85].

Curare has little effect on the central nervous sys-

tem and thus allows the integrity of the senses and volition to be maintained [53,242]. Excitation of the motor nerve terminal is also normal [144]. By analyzing the steps in neuromuscular transmission that could be influenced by curare, it is possible to match some of the predicted effects with experimental observations. In this example, we consider a motoneurone firing at a hypothetical rate of 20/sec. Acetylcholine is released from the pre-synaptic nerve endings and except for the possible situation of continuous, high frequency nerve stimulation [36,154], its stores are probably adequate. In the presence of curare, the evidence is mixed as to whether the transmitter quantal content is maintained during muscle activation [17], or "runs down" [131]. Following diffusion across the synaptic gap, the ability of acetylcholine to form agonist-receptor complexes will be determined by the number of accessible "unblocked" receptor sites. The subsequent increase in membrane permeability to sodium and potassium produces an end-plate potential. It is composed of multiples of miniature end-plate potentials [92] which are 0.4 to 1.0 mV in amplitude and are believed to represent the depolarization resulting from a single quantum of acetylcholine [34,73]. When the end-plate potential is of sufficient size to reach threshold, the muscle cell is excited.

Due to the composite nature of the end-plate potential, it can theoretically be modified by either changes in

the amount of acetylcholine or alterations in its post-synaptic receptor. The mammalian neuromuscular junction is constructed so that ordinarily there is a direct coupling of motoneurone action potential and motor unit twitch. (1) The neuromuscular junction receives only excitatory stimuli unlike synapses in the central nervous system [155] and crustacean motor systems [83] which integrate both excitatory and inhibitory influences. (2) Acetylcholine is released in saturating quantities [74]. (3) Only 25% of the post-synaptic receptors need to be available to ensure end-plate depolarization [208]. (4) The absence of a refactory period for the end-plate allows the frequent miniature end-plate potentials to summate [85]. (5) The rapid breakdown of transmitter by acetylcholinesterase prepares the end-plate for the arrival of another volley of acetylcholine.

Excitation of the muscle cell results in propagation of an action potential along the sarcolemma. The details of the shape of the action potential, the compound action potential, and the overall interference pattern were addressed in the previous discussion section. What matters at this point is that the end-plate potential determines the all-or-none property of muscle fibre activation.

Neuromuscular transmission has a remarkable "margin of safety" consisting of both excess transmitter and receptor. Defined by Paton and Waud [208] as "the extent of interference with the synaptic mechanism that can exist

without failure of transmission", they determined the increase required in the concentration of the agonist (succinylcholine) in the presence of an antagonist to preserve the normal maximal muscle twitch. Expressed in functional terms, partial paralysis was evident only when 75% of the receptors were antagonized. At 90% receptor occlusion, there was no twitch with maximal nerve stimulation delivered every 10 sec. Two important implications are that muscle function would not appear compromised provided there was at least 25% normal transmission and that once neuromuscular block occurs, additional small increases in curare concentration would produce large reductions in muscle force.

If the end-plate potential can depolarize by 10-20 mV, it will have reached the threshold and generate an action potential. Hyperpolarization of the resting membrane, which inhibits the action potential, indicates that nerve stimulation usually produces an end-plate potential of 35-40 mV [34]. This is additional evidence of the large margin of safety. Curare reduces the size of the miniature end-plate potentials [92] without altering the resting potential of the post-synaptic membrane [91], and it is by this mechanism that we understand the failure to reach threshold. At the point of abolition of action potentials in amphibian muscle, Eccles and associates [85] measured the end-plate potential to be 2-4 mV. This would be consistent with the findings of Paton and Waud [208] that with apparent

complete paralysis, there could still be some viable receptors.

In relation to the observations of this investigation, interest lies in that region of receptor blockade where, according to Paton and Waud, muscle function with maximal activation is just normal but a significant proportion of the receptors are occluded and extends to a point where maximal muscle tension has been reduced to approximately one half. An analysis will first be made of events as they pertain to a single muscle fibre. This will then be expanded to the situation in a motor unit followed by that relating to a whole muscle.

Single muscle fibres. If in the motor end-plate of a single muscle cell 75% of the receptors are blocked, the fibre continues to be depolarized with each volley of acetylcholine, eliciting action potentials and twitches. For this discussion, it will be assumed that 0.4 and 40 mV represent the end-plate depolarization due to a single quantum of acetylcholine and a normal nerve volley respectively [92]. With 25% of the receptors providing just complete neuromuscular transmission, the excitation threshold is calculated as 0.25 x 40 mV = 10 mV. Constancy of acetylcholine supply and receptor occlusion should maintain the contractile ability of this fibre. There is some evidence however that high

frequency stimulation of the motoneurone can reduce the availability of acetylcholine [36,154] in the absence of curare. Therefore with submaximal block there might be an apparent increase in weakness independent of any change in the level of receptor occlusion. Curare though is known to aggravate this condition either by creating the situation where transmitter rundown can be evident, or by direct interference with the release of vesicles [103,131,175]. Further increase in the curare concentration itself around the single muscle cell would result in an insufficient number of accessible receptors. Even though a single end-plate potential in this latter condition would fail to reach threshold, two rapidly succeeding miniature potentials (within 20 msec) could combine to reach the firing level [85]. Thus by increasing neural drive, several additional twitches might be possible before transmitter depletion occurs.

In the events described, an action potential must precede each twitch, but it is doubtful that conditions remain static as indicated. Rather there is likely to be a continuous competition between acetylcholine and curare for the receptor which produces a constantly changing end-plate potential. It may occasionally be above threshold and at other times not reach it. In addition, the shape of the end-plate potential is subject to variation. Changes in rise time, duration, and decay time with curare and

prostigmine (acetylcholinesterase inhibitor) compared to control [34,85,92], suggest an influence from the spatial and temporal distribution of local currents. If the muscle force-stimulation frequency relationship applies for single fibres as it does for whole muscles, neuromuscular block would cause marked fluctuations in tension due to the interruption of excitation.

Single motor units. Progressing to one motor unit, the events of the motoneurone terminals and their post-synaptic end-plates can be assumed to be identical to those outlined above. Either there is complete coupling between acetylcholine release and twitch or there is none. Between the motoneurone and its muscle fibres as a whole, the relationship will be less clear cut. First, neural drive may be rhythmic, as shown to occur in paralyzed diaphragms of cats [243], but not all the fibres need necessarily twitch or "miss" at the same time. The average amplitude of twitch tension could be reduced by neuromuscular block to one half but repeated measurements would likely show statistical variation about the mean. Secondly, action potential counts would parallel the number of contracting fibres however the compound action potential of the motor unit might alter in height and shape due to a continuous change in the spatial distribution of the source potentials, even with tension

remaining constant. Thirdly, overall motor unit force could be reduced for two reasons during brief intervals of excitation, (i) a particular fraction of fibres are [illegible] due to neuromuscular block and (ii) because of the [illegible] nature of the block, those fibres still active may [illegible] to achieve or maintain the motoneurone firing frequency. The latter would produce a level of force somewhat less than the fusion of uninterrupted twitches usually generates.

The accompanying figures may be useful in predicting the consequences of intermittent impairment. Figure 38 is redrawn from two graphs of Cooper and Eccles [56] which relate the force as a percent of maximum on the ordinate and excitation frequency on the abscissa for cat soleus and gastrocnemius. Soleus is composed predominantly of slow twitch muscle fibres while gastrocnemius is of a more mixed nature. Below the abscissa is the corresponding cycle time for the frequencies indicated. For this particular discussion, information from whole muscle will be assumed to reflect directly the behaviour of its motor units. Figure 39 indicates time on the abscissa and firing frequency on the ordinate. The curves relate these two variables according to the firing impulse number. Given that any motor unit is depolarized first at time = 0, the time of the second impulse is indicated by curve 2 according to the excitation frequency of that unit. For a motor unit driven at 40 Hz, the second impulse arrives 25 msec after the first. The

third impulse arrives after 50 msec. The lower part of Figure 39 indicates effective durations through which neuromuscular block might occur in a given motor unit, that is, during which no fibre depolarization will take place. Since the literature does not seem to have quantitative data on the union time of a curare molecule and a particular receptor, some values have been assigned. To construct line "a" of Figure 39, it is arranged that every second nerve volley would be blocked in a fast twitch motor unit being fully driven at 50 Hz. Every other 20 msec interval prevents end-plate depolarization. Therefore for this motor unit, the useful frequency, that frequency producing twitches, has been reduced to an average of 25 Hz which from Figure 38 reduces the force from 90% of maximum to 65%. For the same neuromuscular blockade conditions (blocking time - line a), a motor unit firing at 18 Hz in Figure 39 would not be affected by curare until the third nerve volley when the block coincides with the end-plate potential. Thus that motor unit is able to fire at 18 Hz but only for two impulses. Two impulses do not allow it to reach the force expected of this frequency, then during the interval intended for the third impulse, force decays. These events would make it difficult for motor units to maintain force.

The same analysis as used above can be used to determine the impairment at other durations of neuromuscular block. Lines "b", "c", and "d" of Figure 39 have been

produced with the condition that every second nerve volley is prevented when motor units fire at 30, 20, and 8 Hz respectively. They have been selected according to the upper plateau and steep portions of the force-frequency curves of Figure 38 for a representative fast and slow muscle.

Can the level of motor unit activation be altered in response to neuromuscular block? If so, the form of the alteration may be determined according to what function needs to be preserved. In our experiments, the subjects targeted for specific inspiratory pressures so muscle tension was the regulated function. Another candidate might be muscle length, or some combination of length and tension, muscle stiffness. To increase tension from a submaximal level, muscle can use rate coding or recruitment and it would likely be these characteristics which would be used to circumvent the impairment by curare. Given that most activities do not involve muscle at their tetanic frequencies and that submaximal neuromuscular block is inconsequential when very low force levels are required, it is convenient to examine the effects of changes in firing frequency in reaction to neuromuscular block over the steep portion of the force-frequency relationships in Figure 38. Representative frequencies will be selected as 8 and 25 Hz for slow and fast muscle respectively. It will be noticed that in these ranges, small changes in frequency result in

large but linear changes in tension. Figure 39 may be regarded as depicting frequencies which could avoid the effects of the block. In this respect, a given frequency change is more successful at avoiding the block if the modification is made in the low frequency range. Here, each of the impulse number curves are flatter and successive impulses should be able to be produced at a rate which allows the impulse to occur during the unblocked interval. In contrast, in the steeper portion of the curves of Figure 39, impulses are concentrated into blocked or unblocked intervals. By reducing firing frequency, it seems that the probabilities of producing a twitch for each nerve volley could be improved. Furthermore, nerve firing frequency is reduced which reduces the likelihood of acetylcholine run-down. Increasing the excitation frequency would cause large fluctuations in muscle tension due to continuous interruption of the train of depolarization.

Whether muscle can act this way is not known, but by reducing excitation rate, overall tension must be made up by an increase in motor unit recruitment. This implies that more fast twitch units would be activated at lower than usual levels of total muscle tension. But if these units are subject to the same frequency regulation as speculated above, they then contract at slower rates than when they are usually recruited and consequently produce less tension. This could add a further impetus to recruitment.

For much of the above discussion, several assumptions and conditions were used to predict some of the effects that might occur at levels of organization below that of the whole muscle when neuromuscular block is induced. This results because most of our knowledge of the nature of curare's impairment comes from (i) isolated muscle, and in situ experiments in animals, and (ii) the anaesthesiological literature which essentially is descriptive of curare's overall effects.

From the latter however, it is known that the frequency of muscle stimulation is of prime importance in determining the extent of function during curarization. While simple twitches and low excitation rates may indicate recovery, tetanic frequencies reveal that a marked impairment still remains [89,105,110,264]. This can be expressed as "fade" in either the EMG or muscle force and presumably reflects the sensitivity of the neuromuscular junction to acetylcholine rundown when curare is present.

Earlier, it was implied that curare produces an "on" or "off" effect on the neuromuscular junction. It might better be described as unstable for two reasons. First, neither the "on" or "off" condition is likely to appear with any regularity. Secondly, it is known that curare produces "jitter" at the neuromuscular junction. Using a needle multi-electrode, Ekstedt and Stalberg [87] measured the time interval between the action potentials of two muscle fibres

belonging to the same motor unit. Under control conditions, the standard deviation or "jitter" of the mean of this interval was 10-30 usec. At a curarization level just sufficient to produce diplopia, the jitter increased by 5-15 usec. With additional curare, the jitter increased further to 40-80 usec. Occasionally there was complete blocking of one of the potentials in the pair. Subsequent computer simulations [104] suggested that jitter with curare could be explained by variations in the rise time of the end-plate potential, and/or changes in the depolarization threshold.

Whole muscle. Much of our understanding of the behaviour of skeletal muscle and the respiratory muscles is derived from observations during maximal activation of either the muscle fibre, the motor unit, or the whole muscle. Twitch and tetanic tensions, their ratio, speed of contraction and endurance ability all define muscle character [52]. As introduced in the previous discussion section however, muscle is usually engaged in submaximal levels of contraction, and especially so in breathing. The volume of literature on this aspect seems relatively small but several investigations have examined the behaviour of various constituents of muscle with respect to the whole entity [76,161,215,247,267] which suggest significant interactions between the parts. Since inactive muscle does not contribute to producing

force, it becomes part of the load which the active component must move. This is of little concern provided the load is brief or muscle has the reserve to continue the effort for prolonged periods of time.

During curarization there is less active muscle and to perform external work, that part must overcome an increased load. One aspect of this impairment was addressed by the investigation of Pengelly and Rigg (unpublished observations). They found that when the anterior tibialis of the cat was partially paralyzed, it had a length-tension relationship which was the same as the uncurarized muscle when it was submaximally stimulated. Compared to the maximally excited control condition, the optimum length for tension remained the same but curare caused the descending portions of the tension curve to intercept the length axis at a longer position. Because the force decrement with curare was not proportional at all lengths, the effects appeared to be accentuated with muscle shortening. This was suggested by Saunders and his associates [232] to be a possible reason for the marked decrement in inspiratory capacity relative to the weakness indicated at longer respiratory muscle lengths.

The inability to produce force by shortened curarized muscle is supported by several lines of evidence in uncurarized muscle. These suggest progressive difficulty in exerting tension at short lengths unless muscle activation is increased. (1) Twitch-tetanus ratio decreases with

reductions in muscle length [161,247]. (2) There is photographic evidence of myofibrillar deformation at short muscle lengths [254]. (3) De-activation by fatigue and neuronal branch lesion reduce the muscle length over which force can be produced [266]. (4) Tension can only be produced at short muscle lengths by increases in stimulation frequency [215]. One theory of length-dependent de-activation proposes that shortening distorts the transverse tubules and inhibits the inward spread of depolarization [215]. Caffeine promotes calcium release from the sarcoplasmic reticulum and has been shown to increase muscle force at short lengths [226].

Since partial neuromuscular block limits normal muscle shortening, the amount of length-dependent "de-activation" would be assumed to be less than present in the unparalyzed muscle at its shortest length. The failure to produce force might then be related to an inability to overcome internal resistance to length changes exerted by surrounding connective and inactive contractile tissue. Consistent with this notion is the observation that partially curarized muscles take longer to reach twitch tensions [160].

V.B.b. Effect of curare on respiratory muscles in man

Up to this point, evidence has been presented which suggests that curare limits the number of motor end plates able to depolarize and that this is expressed as a reduction of maximal muscle force. The observations reported here in human respiratory muscles must now be interpreted in light of such information and their sources.

Based on their findings of a disproportionate reduction in inspiratory capacity compared to maximal inspiratory pressure at the end-expiratory position, Saunders and coworkers [232] speculated that curare caused an unequal distribution of weakness which would be evident if particular muscles were maximally activated only for particular respiratory manoeuvres. If this was the case, we expected that the EMG in the uncurarized muscle would be maximal only during the effort for which it was fully recruited. Following partial neuromuscular blockade, the EMG would be reduced to its greatest extent when the same manoeuvre was attempted.

The two most outstanding features of the EMG response to static inspiratory pressure in the curarized condition were the reduction in the maximum amount of EMG recorded with maximum pressure and the exaggerated EMG levels for a particular degree of effort. We believed that measurements of only maximum EMG and pressure were unreli-

able given the possibility of "nonspecific activity" [44]. It was therefore necessary to ensure the specificity of the EMG and this could be achieved by graded levels of pressure. We could be confident that the maximum EMG truly reflected the respiratory activity of underlying muscle if it was continuous with that measured during less strenuous efforts. This aspect was more important than could have been anticipated as will be shown below.

With curarization, both maximal pressure at all lung volumes and the maximal EMG were decreased. Those muscle fibres whose motor end-plates do not reach the depolarization threshold will not elicit an action potential and consequently not twitch. As indicated in the previous discussion section, the relationship between EMG and force need not necessarily be linear, however, gross differences between the reduction in myoelectricity and pressure would not be expected. Bigland and her associates [23] showed in rabbit tibialis anterior, that the rectified electromyogram during maximal stimulation decreased as a linear function of twitch tension with progressive curarization.

We hesitate in making such a comparison because the EMG-pressure curve during partial neuromuscular block was not simply an interpolation of the original relationship. In 39 of 60 comparisons, the slope of the EMG increase became more steep and suggests that additional mechanisms were operating. One of several changes, or their

combination, may have been responsible.

Reasons for increased EMG. First, the EMG of the respiratory muscles may have been contaminated by that of other muscles. As discussed in an earlier section, our placement of the electrodes might allow the pectoralis major and the platysma to interfere with the recording of the EMG of the parasternal intercostals, and the scalenes and sternomastoid respectively. This might have occurred with maximal efforts but considering that our subjects were relatively well-trained in performing these manoeuvres, and that these muscles were also curarized, we doubt that these muscles would have been increasingly activated with even the relatively less strenuous pressures. In the case of the diaphragm, no other muscle contaminates the EMG except the heart, but its component was removed in both conditions.

Secondly, the increased rectified EMG might be due to an alteration of the muscle fibre action potential. According to Katz, [146], curare has no effect on the end-plate depolarization threshold nor on the rate of rise and height of the spike. If the conduction velocity of the action potential along the sarcolemma is slowed, as occurs in some instances of fatigue, the EMG contains more low frequency components which are subject to less filtering by intervening tissue [168,248]. This would increase the

rectified value.

Simulation studies have shown that when action potential cancellation is reduced by synchronous muscle fibre excitation, the rectified EMG would be greater than that associated with motor units firing in a more typical asynchronous pattern [195,212]. Or, the procedure can work in the opposite direction. By increasing asynchronization, muscle fibre action potentials of opposite polarity will be more evident as discrete events. Available evidence suggests that this is likely due to variable delays at the neuromuscular junction [170,244] which results in prolonged rise times of end-plate potentials.

Thirdly, it is possible that neural drive to the muscles was augmented during the weakness resulting in either increased frequency of stimulation or motor unit recruitment. DeTroyer and his co-workers [68] found that during curarization, the diaphragm EMG was significantly elevated due to the exertion of greater tension. For all respiratory manoeuvres, abdominal pressure was greater which increased the transdiaphragmatic pressure. We observed that abdominal pressure was also greater for a given inspiratory pressure so our EMG findings are consistent. From the changes in the transdiaphragmatic pressure, DeTroyer's group [68] suggested that the diaphragm took over the effort of breathing and this was supported by a marked reduction in the intercostal and scalene EMG. In contrast, our

measurements clearly show that there was increased intercostal/accessory muscle EMG. Either, we reject the notion that increased diaphragm EMG reflects greater activity or, accept it with the proposal that the same applies for the intercostal/accessory muscles.

If all the respiratory muscles were electrically more active, why was there not more pressure then, in line with the control EMG-pressure relationship? If there was an increase in the internal muscle resistance, then more muscle pressure would have been needed to overcome the load before alveolar pressure could be reduced. Reduced lung and/or chest wall compliance or an uncontrollable increase in expiratory muscle activation might also have produced this result. As far as elastance of the respiratory system is concerned, only subject 2 showed measurable increases, that being due to a reduction in lung compliance. Thus, this aspect could only have a minor role. Antagonistic muscle contraction might have been detectable with electromyography but no reason is known that would lead one to expect this event.

Fourthly, it seems as though in this compromised condition, there was a dissociation of muscle electrical and mechanical events. Some evidence in the clinical literature indicates that this is possible.

Epstein and Epstein [89] recorded both the electromyogram and tension from the thumb adductor during

curarization and recovery. In ulnar nerve stimulations producing a twitch, tension was always reduced to a greater extent than the amplitude of the compound action potential. They were decreased by 81 and 66% respectively at the time of greatest weakness. A replot of their EMG relative to twitch tension shows that the curve is identical to that found by Bigland and her associates [23] in cat tibialis anterior. The action potential decreased very little with the initial muscle weakness but as the latter progressed, the EMG decreased more rapidly. However this is the same investigation reported earlier, in which the "integrated" EMG decreased linearly with the reduction in tension. Therefore, except at the control point and the point of greatest weakness where the two were the same, the height of the compound action potential was greater than the rectified value. The difference was not resolved. The results of Katz [148] are consistent with those of Epstein and Epstein. Two other reports [32,145] also suggest that muscle mechanical activity does not correlate with its myoelectrical behaviour but the evidence is less convincing.

An alteration in the contractile properties of muscle with curare could also cause electro-mechanical uncoupling, but we are unaware of any investigations addressing this issue.

In the previous discussion section, it was shown that as the respiratory muscles shorten, the level of EMG

associated with a particular muscle pressure was increased. Therefore a fifth possibility is that during curarization, the muscles operated at a length disadvantage. If this occurred for all the respiratory muscles, it implies that the end-expiratory position produced a lung volume greater than the control level. This is unlikely as will be discussed later.

Finally, the increased EMG at submaximal pressures could be due to the recruitment of large fibre motor units which normally only become activated with greater muscle pressure. It was shown earlier how curare might promote a reduction in the average firing rate of a motor unit. The marked increase in low frequency components of the EMG frequency spectrum following curare administration is consistent with this notion [222]. For a given level of motor neuron activation, the pertinent muscle fibres produce less force, similar to the reduction observed in tension of the adductor pollicis when it is stimulated at increasing frequencies with submaximal voltage levels [24]. Since, the subjects only feedback was the alveolar pressure he was producing, muscle drive would increase until the target was achieved. Therefore additional motor units would be called upon, these also being limited in their firing frequency. The EMG accompanying large fibre, high threshold, motor units then combines with that already present to elevate the rectified level. The effect would be particularly marked if

motor units could only function at the lower portion of the sigmoidally shaped force-frequency curve. Here increases in discharge rate increase the rectified EMG linearly but tension changes minimally.

Alternatively, the kinetics of curare's inhibition may be such that it allows muscle fibres of motor neurons driven maximally to discharge at near tetanic frequencies for brief intervals. If they operate on the upper flat portion of the force-frequency curve, EMG increases again with rate but the tension gains are small. Furthermore, the tension potentially available at that frequency may not be reached because muscle force lags behind the electrical events [206]. For example, if cat triceps surae muscle is stimulated sinusoidally at a rate from 5 to 30 Hz, tension is only 50% if the cycle occurs 3 times/sec compared to the tension produced when the cycle time is 1 sec.

Two clinical reports have also noted an augmentation of the EMG response to graded muscle force. Lenman [159] explained that the steep EMG/tension curve in patients with poliomyelitis and muscular dystrophy reflected decreased neuromuscular efficiency similar to that seen in healthy but fatigued muscle. Patients with disease of the nervous system were unable to produce high levels of force but the EMG increases were similar to normal muscle.

During tests of elbow flexion, some hemiparetics demonstrated an increased EMG response to force in the

affected limb compared to the normal side [250].

Mechanics of respiratory system. In the study reported here, electromyographic techniques were used to investigate the relationship between inspiratory capacity and the maximal static inspiratory pressure during curarization. Saunders and his associates [232] observed that the two were reduced proportionately while it was predicted that the inspiratory capacity should be relatively more preserved. Due to the very low compliance of the lung at high volumes, large reductions in transpulmonary pressure would be expected to produce only minimal changes in the maximum inspiration. Only some of the observations reported here concur with those of the Saunders group. In two subjects, the curve relating the maximal static inspiratory pressure with lung volume was shifted during curarization in a parallel manner from the control position. The other three subjects behaved according the predicted model, preserving inspiratory capacity. Examples of these findings were shown in the results section. To a certain extent, it might be argued that volume is protected over pressure in all subjects because, as a percentage of the control value, it is decreased less (Figure 40). The mean slope of these lines is -1.93. However, from the comparison in this figure, which should be described as the weaker group? The three

individuals who preserved inspiratory capacity actually show a greater reduction in the maximal static pressure than the first two.

The data of Figure 40 has been transformed to muscle pressure and in Figure 41 was plotted as that determined at the inspiratory capacity position against the value at the relaxed end expiratory position. The two groups retain their relative placement on the graph, but there is evidence of further weakness for all subjects according to the downward shift along the ordinate. The mean slope is now -0.97. This suggests that at least over a lung volume range equivalent to the inspiratory capacity during submaximal curarization, the extent of paralysis is similar at long and short muscle lengths. Elsewhere in this discussion, it was shown that this may not apply at very short muscle lengths.

To identify the mechanical factors which could explain these observations, the partially curarized respiratory musculature will be treated as a pumping system. According to Mead and Milic-Emili [181], attention should focus on the medium to be pumped, the passive elements that couple an energy source to the medium, and the energy source itself. Because quantitive electromyography precludes consideration of dynamic events, we may overlook the influence of the medium. Rahn and his co-workers [216] showed that the lungs and chest wall comprise the passive elements and that the energy source is derived from the respiratory

muscles.

The extent to which alveolar pressure can be reduced when the airway is closed depends on the force of the respiratory muscles and their ability to overcome the elastic recoil of the passive elements. Thus, -Palv = -Pmus +Pw +Pl. Because at the end expiratory position the chest wall recoil outward is equal to the lung's recoil inward, most of the available muscle pressure would be expected to be evident as the alveolar pressure change. This then offers a useful reference with which to express the extent of respiratory muscle weakness. At the upper volume extreme, the large influence of the passive elements require that muscle pressure itself, rather than alveolar pressure, be determined.

Several factors have been postulated which could prevent the full force available in the respiratory musculature from being evident. (1) Reflex inhibition of motor units may be operating since maximal voluntary efforts fail to achieve the pressure levels observed during spontaneous actions such as coughing and vomiting [45]. (2) From the finding of Campbell and Green [43] that abdominal muscle activity increases near the inspiratory capacity, it is possible that other antagonistic muscles can prevent maximum muscle pressure from being expressed. Mead and his associates [179] however did not concur on this point. (3) It is not known how much muscle pressure is expended in

deformation of various structures in the chest before alveolar pressure is reduced. (4) The different respiratory muscles may not be recruited to the same degree for a given respiratory act. Therefore, it is not surprising that across a healthy population, muscle force itself is not a major determinant of the ultimate level of maximal inspiration [224]. It was one of the assumptions of this investigation that muscle performance at one level of lung volume may not accurately reflect competency at another level. Static tests of muscle pressure and mechanics are recommended to accompany standard spirometry in pulmonary evaluations [49].

In contrast, there are many situations in which muscle force does account for most of the maximal lung volume change once the passive mechanical elements have been considered. First, we consider only the passive component where elastic recoil may change in the chest wall and/or the lung. (1) In the pressure-volume description of the respiratory system, the chest wall may shift its position along the pressure abscissa and/or alter its elastance. The former effect may be produced by pressure breathing in which positive pressure expands the thorax while negative pressure deflates it. The principle is the same as putting weights on top of a bellows [238]. Increases in elastance are produced during chest strapping [66]. For a given strap circumference, the impairment on the chest is greater with

elevations in lung volume. (2) Lung elastance can be increased by atelectasis [40], thoracic restriction [66,234], and redistribution of blood volume to the pulmonary vasculature as can occur with pressure applied to the lower extremities [31]. These examples have been selected because when acute changes are experimentally produced in the passive mechanical properties of the respiratory system of healthy subjects, it may be assumed that the respiratory muscles are not impaired. Yet, the inspiratory capacity is decreased.

In considering muscle force, reference can be made to the decreases in maximal lung volumes observed in neuromuscular diseases [19,29,67,75,107,223,237] and muscle paralysis [69,97,98]. In general, the maximal static respiratory pressures are decreased to a greater extent than the maximal lung volumes.

The interaction of muscle force and the passive elastic elements determine the shape of the active pressure-volume diagram of the respiratory system. First, by locating the end-expiratory position, it marks the starting point for the inspiratory capacity. Secondly, the maximal inspired volume is reached when respiratory muscle pressure is exactly offset by the passive recoil.

The Campbell diagram in Figure 42 illustrates how the end-expiratory position may change. The intersection of the elastic recoil pressure of the lungs and chest wall

determine the control end-expiratory position, point A, at which the esophageal pressure records approximately -5 cm H2O. Acute increases in lung recoil may occur which shift the end-expiratory position downward along the ordinate. Esophageal pressure at this volume will be more negative (Point B). When the pressure-volume relationship of the chest wall is altered in the manner observed by DeTroyer and Bastenier-Geens [65], the end-expiratory position again is decreased but esophageal pressure is less negative (Point C) compared to control. Finally, esophageal pressure may be relatively unchanged even though the end-expiratory position is reduced (Point D) by changes in both the lung and the chest wall.

Having discussed earlier how total lung capacity is determined by the respiratory system elastic recoil and respiratory muscle pressure, this volume represents the uppermost point on the active pressure-volume diagram. Over the maximum inspiratory volume range, the end-expiratory position is the other linking point. From the examples above, physiological changes producing a decrease in the end-expiratory position, could add one litre of lung volume to the inspiratory capacity. Even though muscle weakness severely reduced total lung capacity, the inspiratory capacity would appear preserved, albeit spuriously.

Despite other investigations producing muscle weakness with neuromuscular block of a similar level used in

this study, we still know little of the passive mechanical changes in the respiratory system. DeTroyer and Bastenier-Geens [65] found the functional residual capacity to be decreased by approximately 0.5 l. Inspiratory lung compliance was unchanged but expiratory compliance was reduced by 10%. The relaxed chest wall shifted 4 cm H2O rightward in a parallel manner. Consistent with these is the observation that the end-expiratory lung volume is increased in patients with myasthenia gravis after receiving pyridostigmine [67]. In contrast with anaesthetization and complete paralysis, Rehder and associates [220] found the functional residual capacity to be unchanged.

Although some individual changes in the passive mechanical properties of the respiratory system were found in this investigation, the considerable variation between the subjects, not only in the magnitude of the changes but more importantly in their direction, preclude these as being strongly associated with the reduction observed in lung volume and muscle pressure in all subjects. Only in the end-expiratory position is there likely to have been a change. In 4 of the 5 subjects, the esophageal pressure at this level became less negative. As explained earlier, this suggests a reduction in the functional residual capacity which, by considering the respiratory system's compliance, would amount to 250 ml in these individuals. In the fifth subject, the esophageal pressure at the end-expiratory

position became more negative, and since lung compliance was also reduced, the functional residual capacity may also have decreased.

Not only could this amount contribute to the inspiratory capacity, but by making use of the mechanical advantage derived when muscles are lengthened, the maximum inspiratory pressure may be increased. The extent of the increase however would probably be limited because in this lung volume range the effective elastance is already very low.

Differential muscle paralysis. Up to this point, the passive chest wall, the lungs, and the respiratory muscles have been considered as whole parts. The association of these do not appear to reconcile the differences in the shape of the active pressure-lung volume relationships observed in our subjects. Therefore, additional insights are sought by examining those parts which can be further subdivided anatomically or functionally, namely the passive chest wall and the muscles. Indeed, it was similar [illegible] which prompted the electromyographic assessment of the different respiratory muscles.

During the preliminary stages of this investigation, DeTroyer and his co-workers [68] reported that during quiet breathing and voluntary hyperpnea, submaximal neuromuscular

block produced an increase in the diaphragmatic EMG and a decrease in the intercostal and scalene EMG for breaths of equivalent volume. Furthermore, during inspiratory capacity manoeuvres, a given esophageal pressure change was accompanied by a greater increase in abdominal pressure following muscle weakness. These suggest that the diaphragm was more resistant to the effects of muscle paralysis and accordingly assumed a greater role in ventilation. These results are important but are limited in reference to our investigation. (1) DeTroyer did not measure the effect of submaximal paralysis on the EMG during maximal activation. Consequently, the observations from submaximal breaths may simply show selection of the muscle recruitment pattern requiring the least effort. Consistent with DeTroyer's results however is the earlier finding that curarization produces more abdominal and less thoracic displacement during breathing [232]. (2) DeTroyer recorded the EMG from subjects in the supine position while all data of spirometry and mechanics were collected on a separate day and from seated postures. It is known that with posture changes, there are important differences in muscle recruitment [81,239,260], functional residual capacity, and lung and chest wall mechanics [4,9]. Our finding of a leftward transposition in the pressure-EMG relationship in most muscle comparisons suggest not preferential resistance of particular muscles to curarization rather, nonspecific impairment with all muscles being

susceptible. In agreement with DeTroyer's results, we observed a general increase in the transdiaphragmatic pressure for given esophageal pressure changes. Therefore, any increase in diaphragm EMG reported here may be linked to its heightened respiratory activity or possibly due to increased abdominal contraction causing greater opposition for the diaphragm. If the latter occurred, it might be speculated that any potential elevation of diaphragm EMG during submaximal pressure would have been lessened if it was activated at a longer length. We showed, as have others, that for a given muscle force, muscles produce less EMG when contracting at long lengths. In light of the role of the abdominal muscles in optimizing the diaphragm's mechanical function [111], the diaphragm may have been positioned higher in the thorax. A decrease in the functional residual capacity should then also occur.

The proposition of Saunders and associates [232], that the inability to preserve inspiratory capacity according to their mechanical model was due to the unequal distribution of muscle weakness, would have been supported if we had observed consistent differences among the muscles in the quantity of the integrated electromyogram. Effects due to muscle specificity, lung volume, and degree of weakness were considered but the wide variability in the magnitude of the EMG reductions restrict any confidence in associating the maximum EMG during curarization with the maximum alveolar

pressure produced. There was only a slight suggestion that the diaphragm may be less affected by curare and there were no differences between the subjects that could explain the two maximum pressure-lung volume profiles (Figures 22 and 23).

When the airway is occluded and at least a moderate static effort is produced, there is considerable distortion of the chest wall [233], particularly in the anterior-posterior direction for the rib-cage when the pressure is generated below the relaxed end-expiratory position [8]. Agostoni and Mognoni [8] reasoned that if forces resulting from activity of the respiratory muscles were evenly distributed over the chest wall, the shape of the chest wall should be the same during static efforts as during relaxation. The equilibrium position of various parts of the chest wall would be determined by the net transthoracic pressure, but because there is distortion, the net pressure cannot be uniform. With a static inspiratory effort, the lateral diameter of the rib-cage increases while the anterior-posterior diameter decreases. Therefore the former action is probably produced by muscle activation while the latter stems from the passive response to the pressure across the chest wall and the motion of the lateral parts.

That the extent of deformation of the rib-cage is related to reduced intercostal muscle recruitment is suggested by two lines of evidence. (1) There is no distortion

in subjects breathing against inspiratory loads when EMG is detected in all regions of the intercostal musculature. In those who demonstrated distortion, EMG activity in the parasternal region was decreased [228]. (2) When the intercostal muscles are paralyzed following a cervical lesion of the spinal cord, there is marked paradoxical motion of the rib-cage [59,197].

The underlying explanation for these observations may be derived from a mechanical model. From investigations describing the motion of the chest wall, it is well accepted that during breathing the chest wall has two degrees of freedom with which to produce volume changes [152,239]. The rib-cage and abdomen-diaphragm components of the chest wall are also considered to operate hydraulically in parallel [4]. These properties can be modelled with a single chamber, two cylinder, piston system in which the pistons are driven by the rib-cage and diaphragm muscles respectively [210]. Contracting both sets of muscles is very effective in producing large pressure changes in the system. (An in-series muscle arrangement [76] facilitates volume displacement.) If only one muscle set is activated, the maximum pressure developed in the chamber will be less than the muscle is capable of producing because part of the muscle pressure is wasted on suction acting on the other piston. Assuming that the inactive rib-cage can be represented by the passive piston, the work of breathing for the diaphragm

will be greater [112], and the maximum volume that can be displaced will be less.

The latter point above is particularly relevant to the observations with partial curarization. If the pistons of the two cylinder model are activated to create a constant negative chamber pressure, each set of muscles must maintain a net level of force that produces a pressure difference across the face of the piston equivalent to the chamber pressure. To further mimic the respiratory system, each piston should have elastance. Therefore, in order to contribute to changing chamber pressure, each muscle must first overcome the passive elastance related to the position of that piston. These static characteristics have already been described for the rib-cage and the diaphragm-abdomen [7,153]. When the muscles are submaximally paralyzed, the maximum chamber pressure, i.e. static inspiratory alveolar pressure, will be reduced. If one muscle, or set of muscles, should happen to be more resistant to paralysis than the other, as has been speculated for the diaphragm [68,232], when it is fully recruited the other piston would be drawn inward. The amount drawn would be determined by the effective elastance (see [209] for functional definition) of the weakened piston, which is the sum of the passive elastance and the available active muscle elastance. Only when the weaker piston is operating on a less compliant portion of its pressure-volume characteristic, will it begin

to behave as a more rigid structure. This means that as long as there is distortion of the chamber wall, the maximum force of the less affected muscle cannot be fully realized. In the respiratory system, a paralyzed and highly compliant rib-cage may decrease the effectiveness of the diaphragm to reduce pleural pressure. At the end-expiratory lung position, this would be evident as a weakened static inspiratory alveolar pressure. It is further compounded by the possibility that the still functioning muscle may shorten considerably before any substantial pressure acts on the lung. Then it contracts with less mechanical advantage. During inflation, the decreasing pleural pressure may draw in the rib-cage and reduce the inspiratory capacity more than expected from the available diaphragmatic force. Observations in quadriplegics demonstrate that restoration of reflex activity in the intercostals is associated with an improvement in ventilatory function, that likely resulting from the stabilizing effect on the rib-cage [69,241]. Furthermore, actual measurements show rib-cage compliance is increased after high cervical lesions [59] and during mechanical ventilation of paralyzed patients, there is a greater volume contribution by the rib-cage to the tidal breath [125,257].

In a similar manner, the diaphragm may yield to the decrease in pleural pressure in some instances and move cephalad [171] while attempting to move caudad. In this

investigation, it was not conclusively shown that the extra-diaghragmatic muscles are more affected by curare than the diaphragm. If diaphragm activity is de-emphasized, we would then expect little increase in abdominal pressure during expansion of the lung [70,174].

It follows from the above discussion on the mechanical factors relevant during partial curarization, that a definitive breakdown of inspiratory muscle function cannot be determined until respiratory manoeuvres are analyzed by their precise location on the pressure-volume diagram. Of prime importance is the identification of the end-expiratory position from which all tidal inspiration begins. Earlier it was suggested that this lung volume might decrease with muscle weakness through a decreased recoil of the chest wall outward and an increased lung recoil inward. In view of the inspiratory role of the abdominal muscles [111], it is also possible that the resting lung volume during curarization is increased. If the paralyzed abdominal wall allows the abdominal contents to follow the force of gravity and protrude forward in the upright posture, the diaphragm might passively be in a more depressed position. This would cause a relatively inflated condition for the lung and perhaps reduce the length of the diaphragm muscle fibres. Both would tend to decrease the inspiratory capacity. Secondly, because there can be considerable distortion of the chest wall during muscular contraction, the work done by and the

work done on the rib-cage and the diaphragm-abdomen need to be determined. Analysis of the motion of the parts will assist in explaining the behaviour of the system. An important implication of the fact that chest wall motion has two degrees of freedom is that, in instances of loaded breathing or muscular impairment, the respiratory muscles can expand the chest along the path with the lowest elastance, i.e. offering the least resistance.

The evidence leading many to suggest that the diaphragm is more resistant to neuromuscular blocking agents than other skeletal muscles was noted in the literature review of this thesis and by DeTroyer and associates [68]. This special property has been attributed to differences among muscles in the safety-margin of neuromuscular transmission, fibre-type composition, perfusion, and temperature. Recently, the report of Feldman and Tyrrell [93] has come to our attention. They develop the notion that if curare acts competitively for the acetylcholine receptor, then its action should be reduced if the agonist could displace it. With constant faradization following the onset of neuromuscular block, they observed that recovery from curare in the stimulated arm was more rapid than in the opposite limb. It was believed that the additional acetylcholine explained this as well as the often noted early return of diaphragm function following surgery. That rapid recovery was due to neuromuscular activity antagonizing the

block was also suggested by Brown and co-workers [37]. Indeed, it has been known for many years that curarization [133] and myasthenia gravis [80] offer evidence of post-tetanic neuromuscular facilitation with which muscle twitch tension can be potentiated. As a result of constant phrenic activity, even when the diaphragm is completely paralyzed [243], it is reasonable that the regular release of acetylcholine could account for the delayed impairment and early recovery of the diaphragm with curarization. If so, respiratory manoeuvres performed over the tidal lung volume range might appear only marginally affected while inspiratory capacity tests, which involve other, less active muscles, and perhaps high recruitment threshold diaphragmatic motor units, could show a greater reduction in function. This could be tested by comparing the maximal torques of two muscle systems such as those of the dorsiflexors during partial curarization. Between measurements, the muscles of one limb would remain inactive while those of the other would be producing contractions at frequencies and relative intensities simulating respiration.

CHAPTER VI

SUMMARY

VI. SUMMARY

The experiments reported in this thesis were designed to determine if the intercostal/accessory muscles would be more affected by submaximal neuromuscular blockade than the diaphragm. The rectified electromyograms of the diaphragm, intercostals, scalenes, and sternomastoid muscles were recorded before and during partial curarization controlled by intravenous infusion while subjects produced maximal and submaximal static inspiratory pressures over the inspiratory capacity range. This technique controls for length-tension relationships known to affect skeletal muscle.

In the uncurarized experiments, very low levels of pressure activated only the diaphragm. Further increases in pressure then recruited the other muscles, with the EMG increasing systematically with changes in contraction intensity. Static efforts performed at greater lung volumes augmented the EMG. In relation to the EMG area defined by maximal pressure and volume, resting ventilatory demands would require only a small proportion of the total myo-electric reserve.

Partial curarization decreased the maximal static inspiratory pressure by 62%. According to the maximal level of rectified EMG produced, the reduction for the intercostals and sternomastoid was not greater than that for the diaphragm, although the scalenes did appear to be just slightly more affected. The decrease in the calculated maximal muscle pressure at inspiratory capacity during curarization was in proportion to the change at the end-expiratory position showing that the effects of muscle length, as indicated by volume, are not altered by curarization. Curare caused the pressure-EMG relationship to differ from the control condition in that particular submaximal pressures elicited more EMG in all muscles. This suggested that partial neuromuscular blockade interfered with the conversion of electrical events into whole muscle tension, probably by uncoupling the normal twitch-tension summation process. Because the chest wall has two pressure generators acting hydraulically in parallel, it is also possible that a different weakness level in either of the generators disproportionately reduces the overall intrathoracic pressure.

Consideration of the physiological events at the neuromuscular junction make it likely that the apparent resistance of the respiratory muscles over other skeletal muscles to the effects of curare is due to the persistent activation of their motoneurones by the respiratory centre which then continuously release acetylcholine at the motor

end-plates, rather than due to a property attributable to special metabolic characteristics as others have proposed.

CHAPTER VII

FIGURES AND TABLES

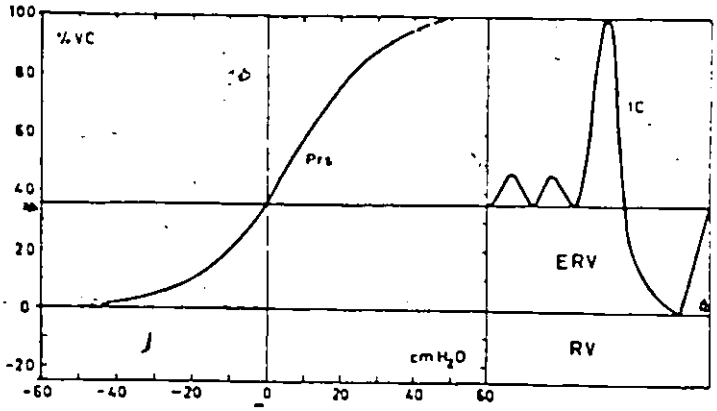


Figure 1. Static volume-pressure curves of the total respiratory system during relaxation in the upright posture, with a spirogram showing the pulmonary subdivisions. The *slanting broken lines* indicate the volume change during relaxation against an obstruction due to gas compression at TLC and expansion at RV. The *curve* was extended to include the full vital capacity range by means of externally applied pressures.

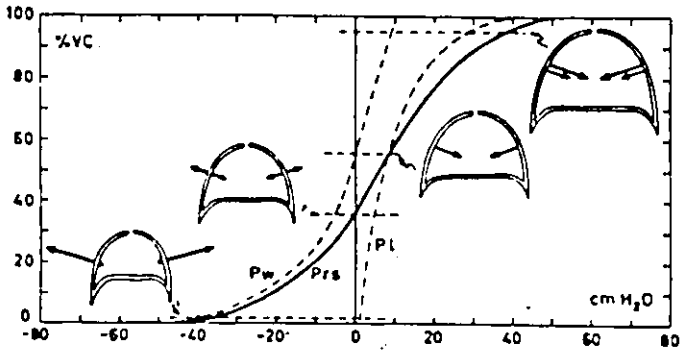


Figure 2. Static volume-pressure curves of the lung, chest wall, and total respiratory system, during relaxation in the upright posture. The static forces of the lung and of the chest wall are pictured by the *arrows* in the side drawings. The dimensions of the arrows are not in scale; the volume corresponding to each drawing is indicated by the *horizontal broken lines*.

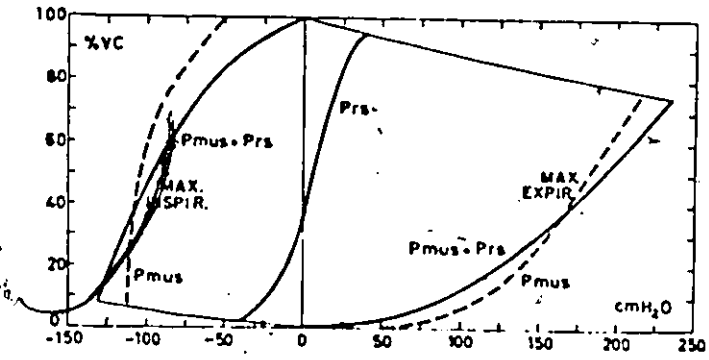


Figure 3. Lung volume against alveolar pressure during maximum inspiratory and expiratory efforts and during relaxation. The *broken lines* indicate the pressure contributed by the muscles.

Figure 4. Scheme for target alveolar pressures over inspiratory capacity range.

Target levels (+) were to cover full range of mouth (or alveolar) pressures.

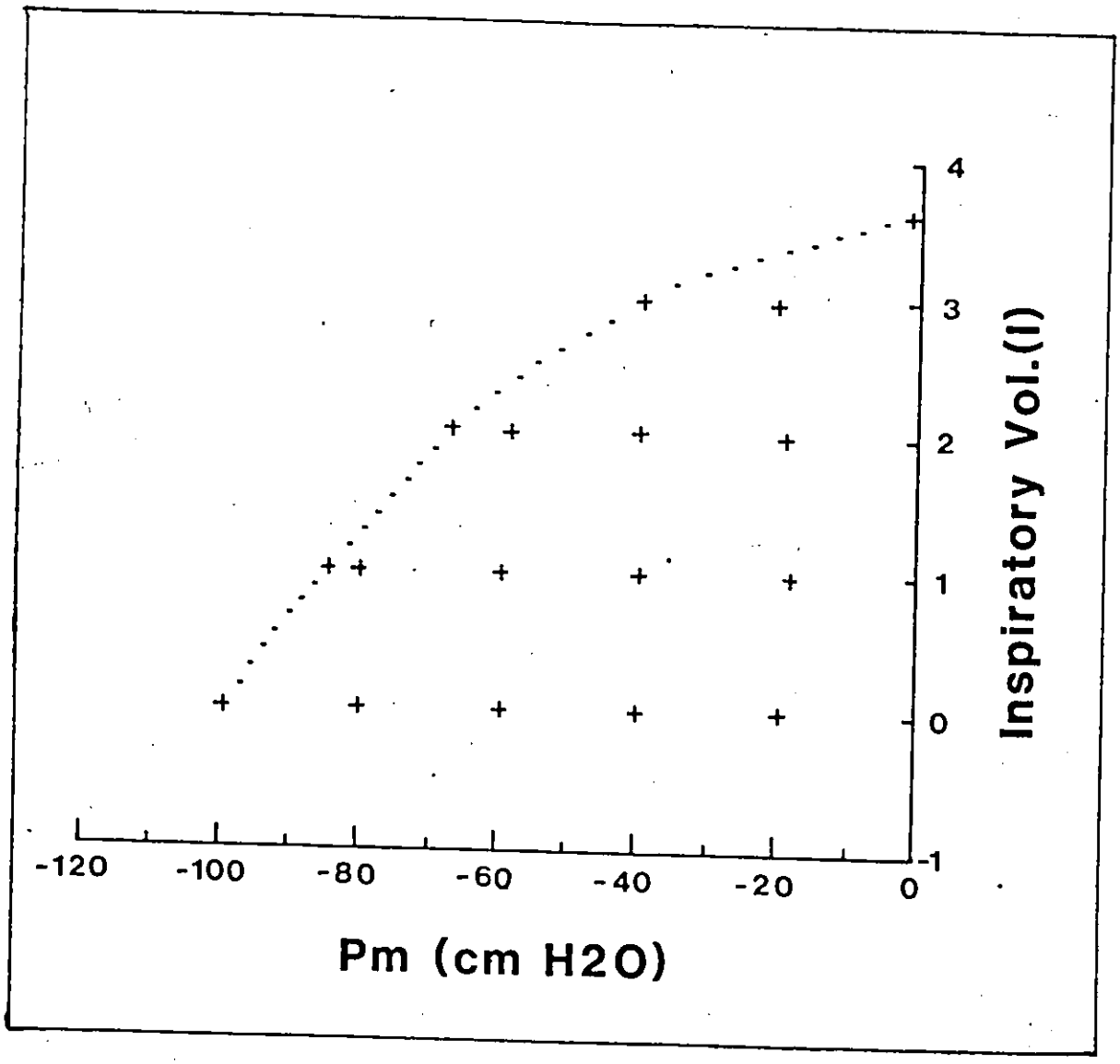

4
3
2
1
0
-1
Inspiratory Vol.(l)
-120
-100
-80
-60
-40
-20
0
Pm (cm H2O)

Figure 5. Sample chart record of measured variables for two consecutive efforts at 1 l above end-expiratory position.

All records are traced over time which occurs from left to right. The measured variables listed from the top are: inspired lung volume relative to end-expiratory position, inspiratory mouth (or alveolar) pressure, esophageal pressure, gastric pressure, smooth-rectified diaphragm EMG (with cardiac artifact removed), smooth-rectified intercostal EMG, smooth-rectified scalenes EMG, and smooth-rectified sternomastoid EMG.

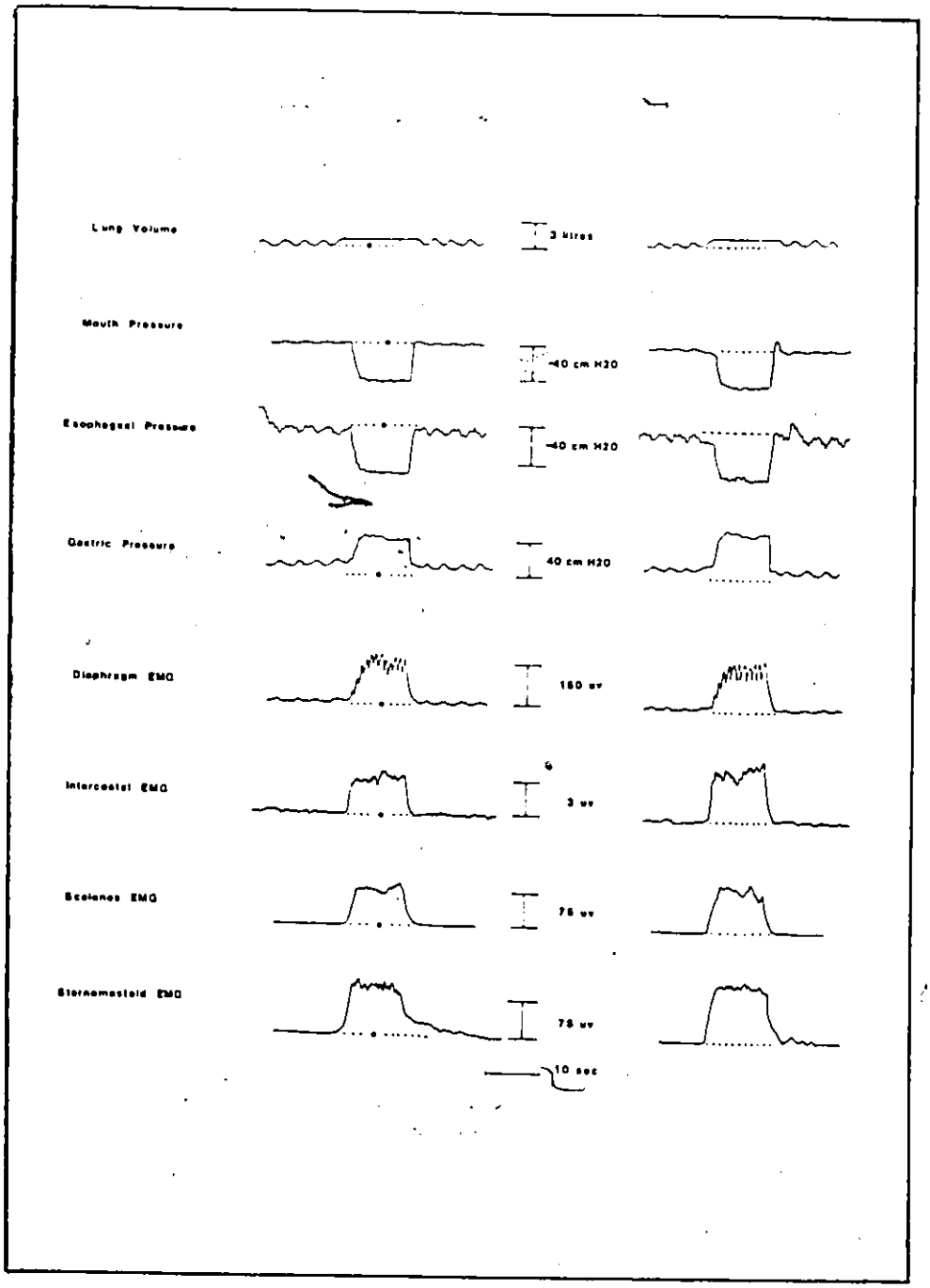

Lung Volume
3 litres
Mouth Pressure
-40 cm H20
Esophageal Pressure
-40 cm H20
Gastric Pressure
40 cm H20
Diaphragm EMG
150 uv
Intercostal EMG
3 uv
Scalenes EMG
75 uv
Sternomastoid EMG
75 uv
10 sec

Figure 6. Sample chart record of measured variables for two consecutive efforts at 3 l above end-expiratory position.

All records are traced over time which occurs from left to right. The measured variables listed from top are: inspired lung volume, inspiratory mouth pressure, esophageal pressure, gastric pressure, smooth-rectified diaphragm EMG, smooth-rectified intercostal EMG, smooth-rectified scalenes EMG, smooth-rectified sternomastoid EMG.

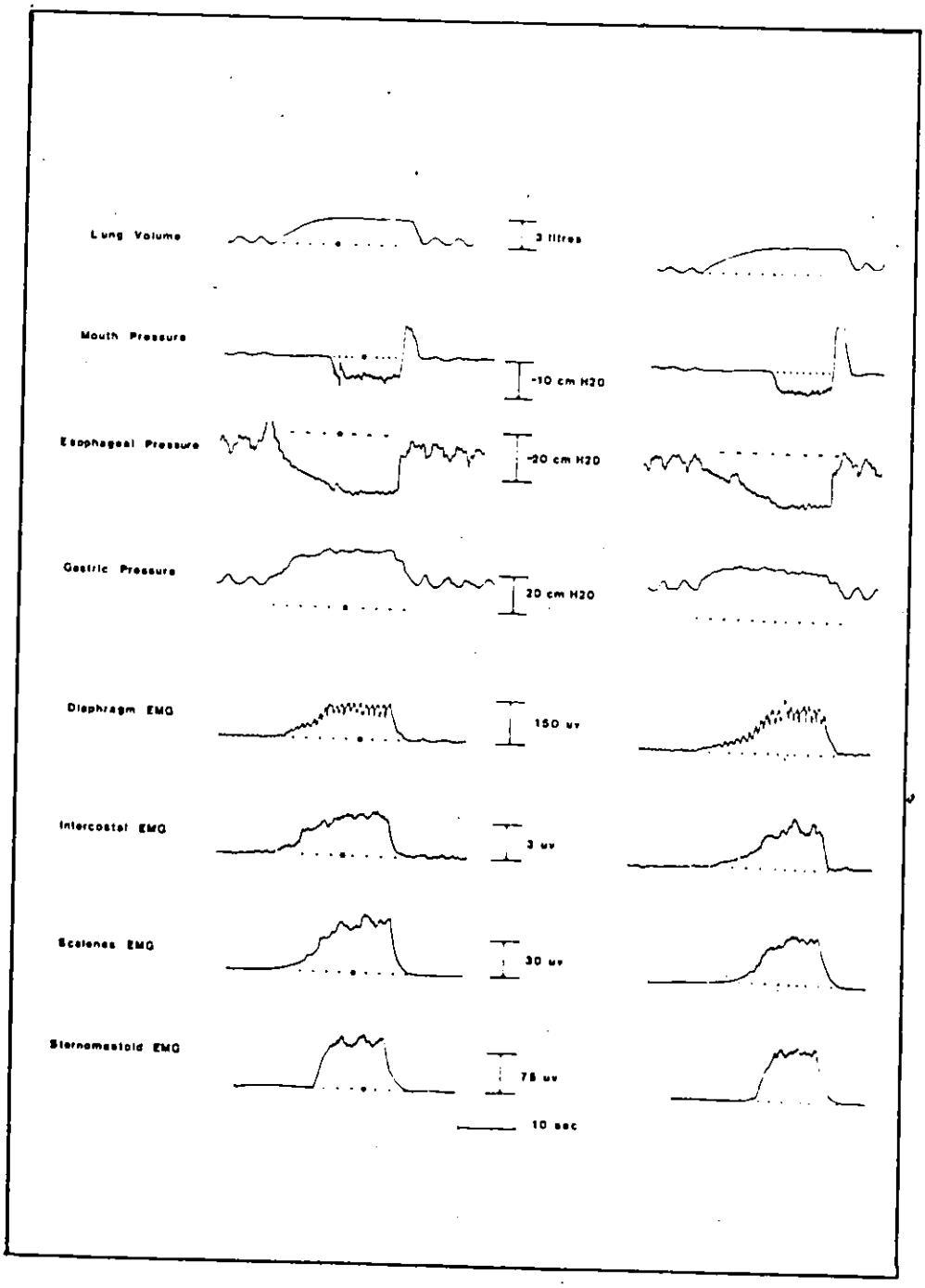
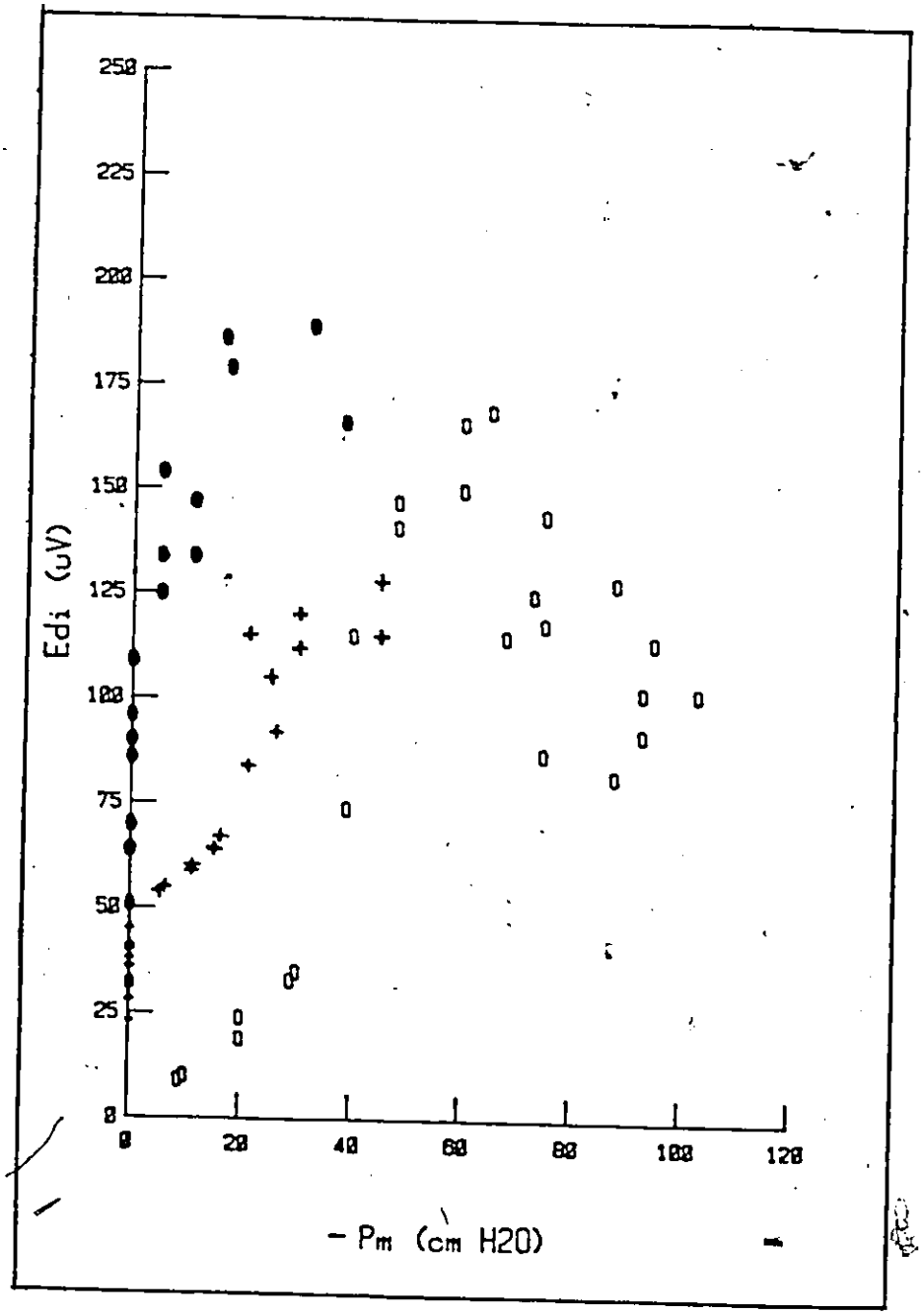
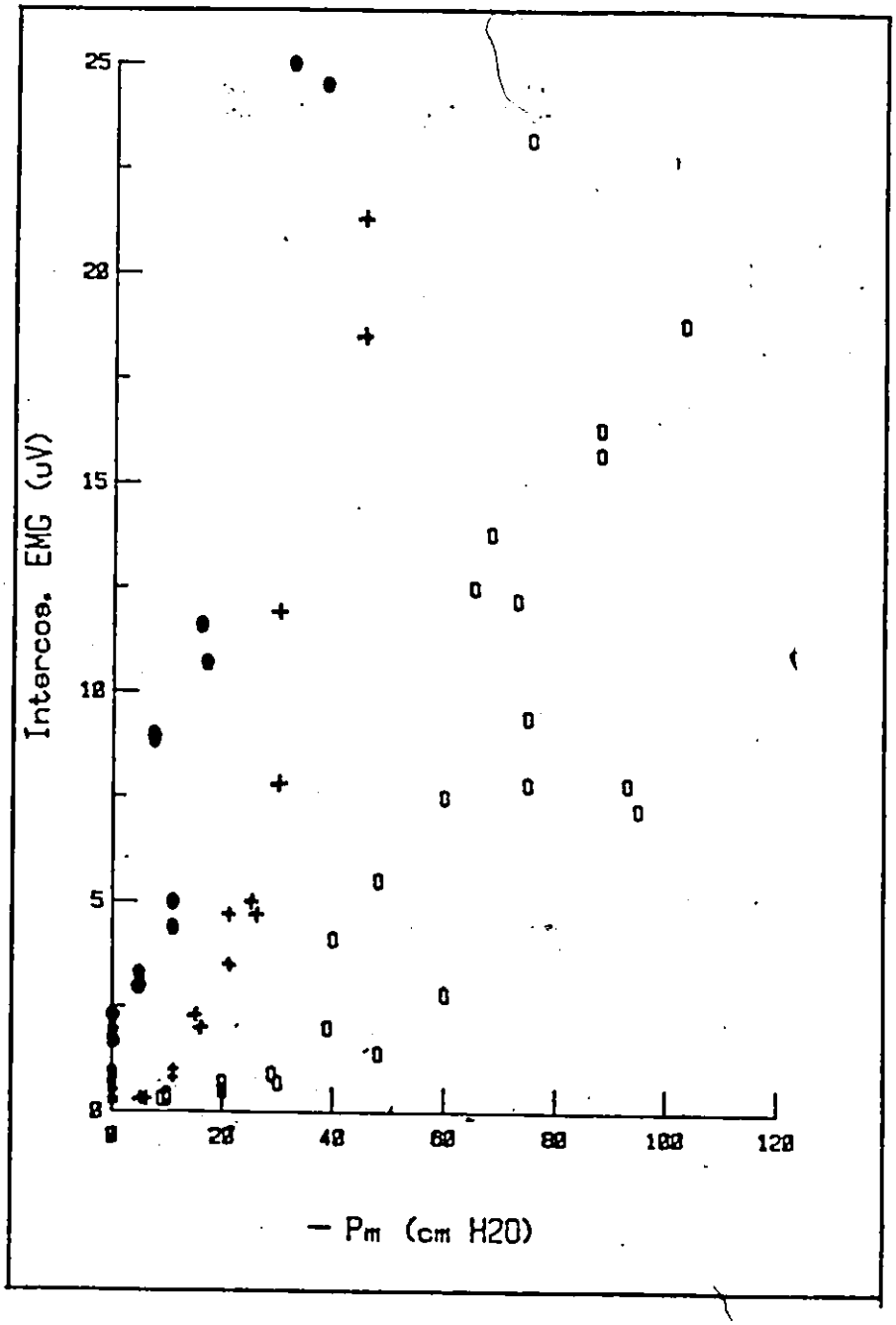
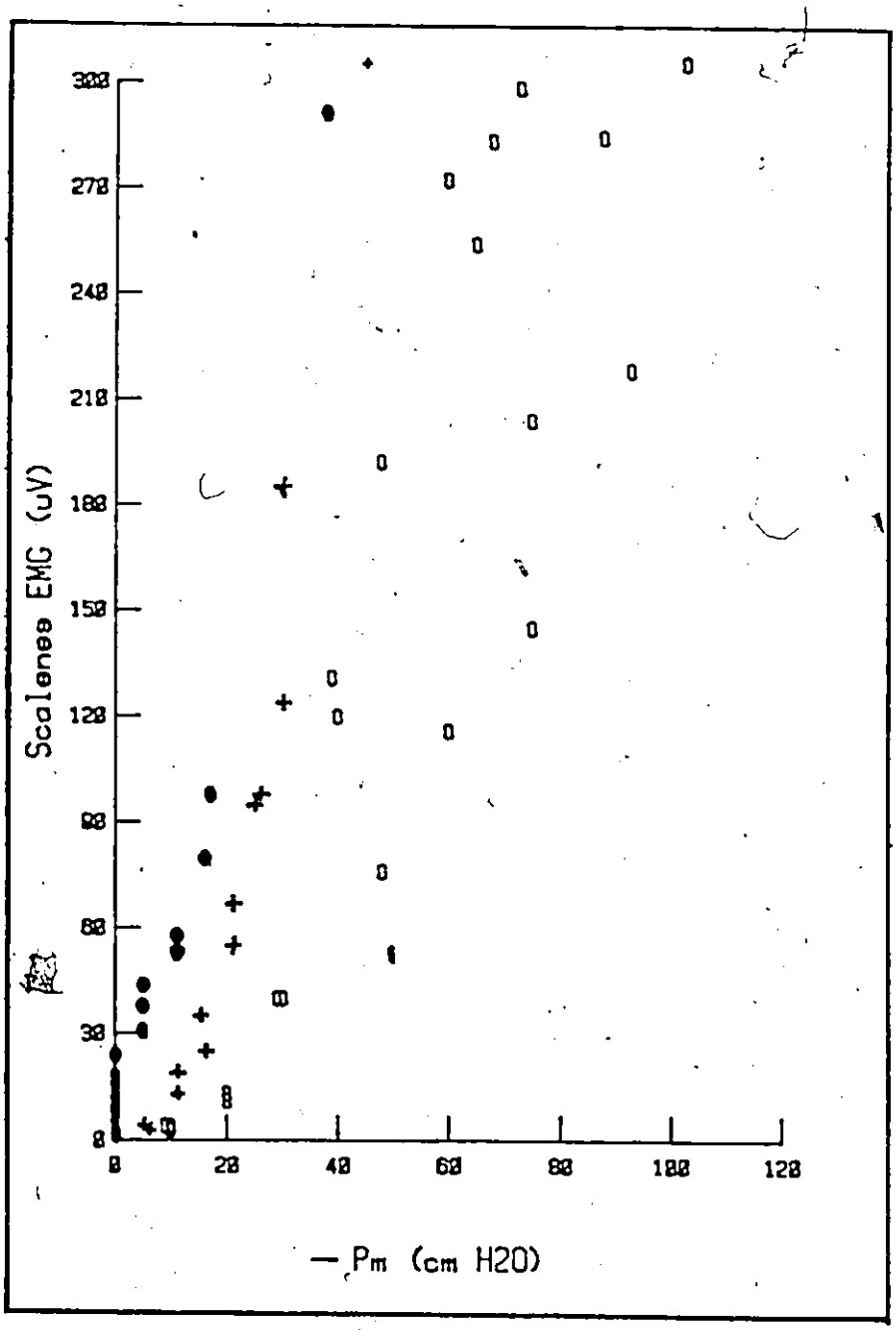

Lung Volume
3 litres
Mouth Pressure
-10 cm H20
Esophageal Pressure
-20 cm H20
Gastric Pressure
20 cm H20
Diaphragm EMG
150 uv
Intercostal EMG
3 uv
Scalenes EMG
30 uv
Sternomastoid EMG
75 uv
10 sec

Figure 7. Rectified EMG of four muscles at different mouth pressures and lung volumes.

Figure 7a. Diaphragm EMG at end-expiratory position (e.e.p.)(symbol o), at 2 l above e.e.p. (+), at 3 l above e.e.p. (●). Figure 7b. Same as 7a except for intercostal EMG. Figure 7c. Same as 7a except for scalenes EMG. Figure 7d. Same as 7a except for sternomastoid EMG.


250
225
200
175
150
125
100
75
50
25
0
Edi (uV)
0
20
40
60
80
100
120
- Pm (cm H20)


25
20
15
10
5
0
Intercos. EMG (uV)
0
20
40
60
80
100
120
— Pm (cm H20)


Scalenes EMG (uV)
300
270
240
210
180
150
120
90
60
30
0
0
20
40
60
80
100
120
— Pm (cm H2O)

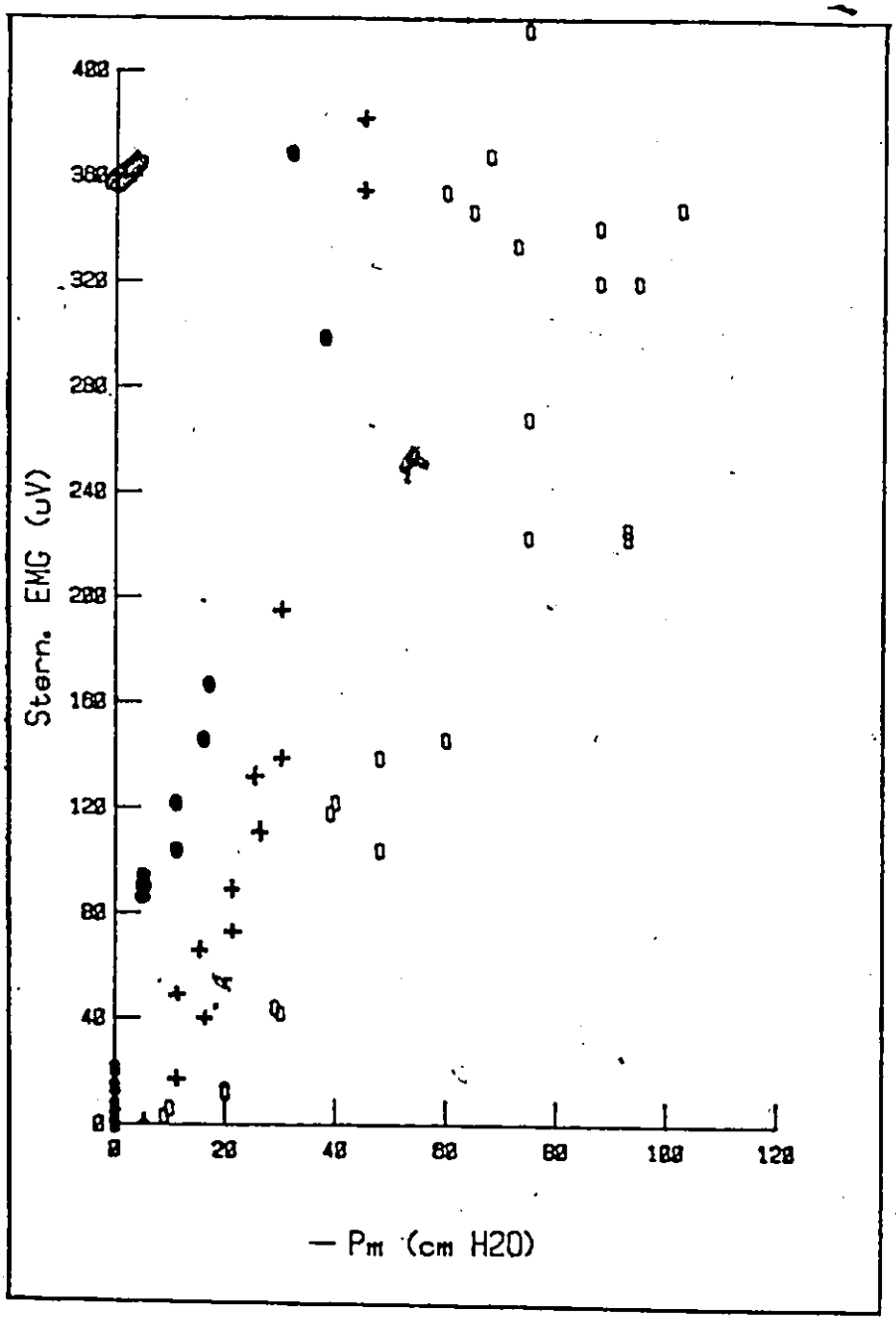
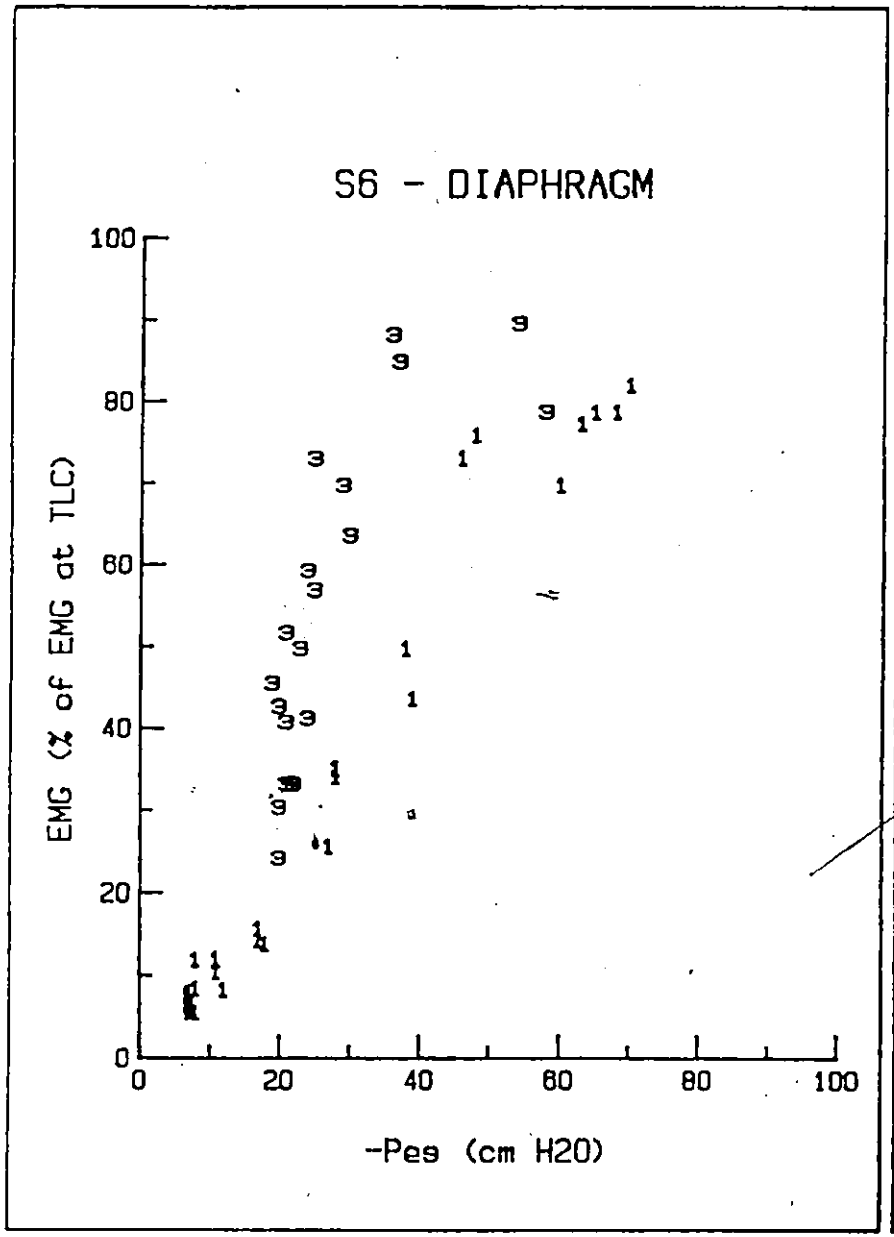

Stern. EMG (uV)
400
360
320
280
240
200
160
120
80
40
0
0
20
40
60
80
100
120
— Pm (cm H20)

Figure 8. Rectified diaphragm EMG for different esophageal pressures at two lung volumes for subject 6 (pg 209).

Efforts at 1 l (symbol 1) and 3 l (3) above e.e.p.

Figure 9. Rectified intercostal EMG for different esophageal pressures at two lung volumes for subject 6.

Efforts at 1 l (symbol 1) and 3 l (3) above e.e.p.


S6 - DIAPHRAGM
EMG (% of EMG at TLC)
-Pes (cm H20)
0
20
40
60
80
100

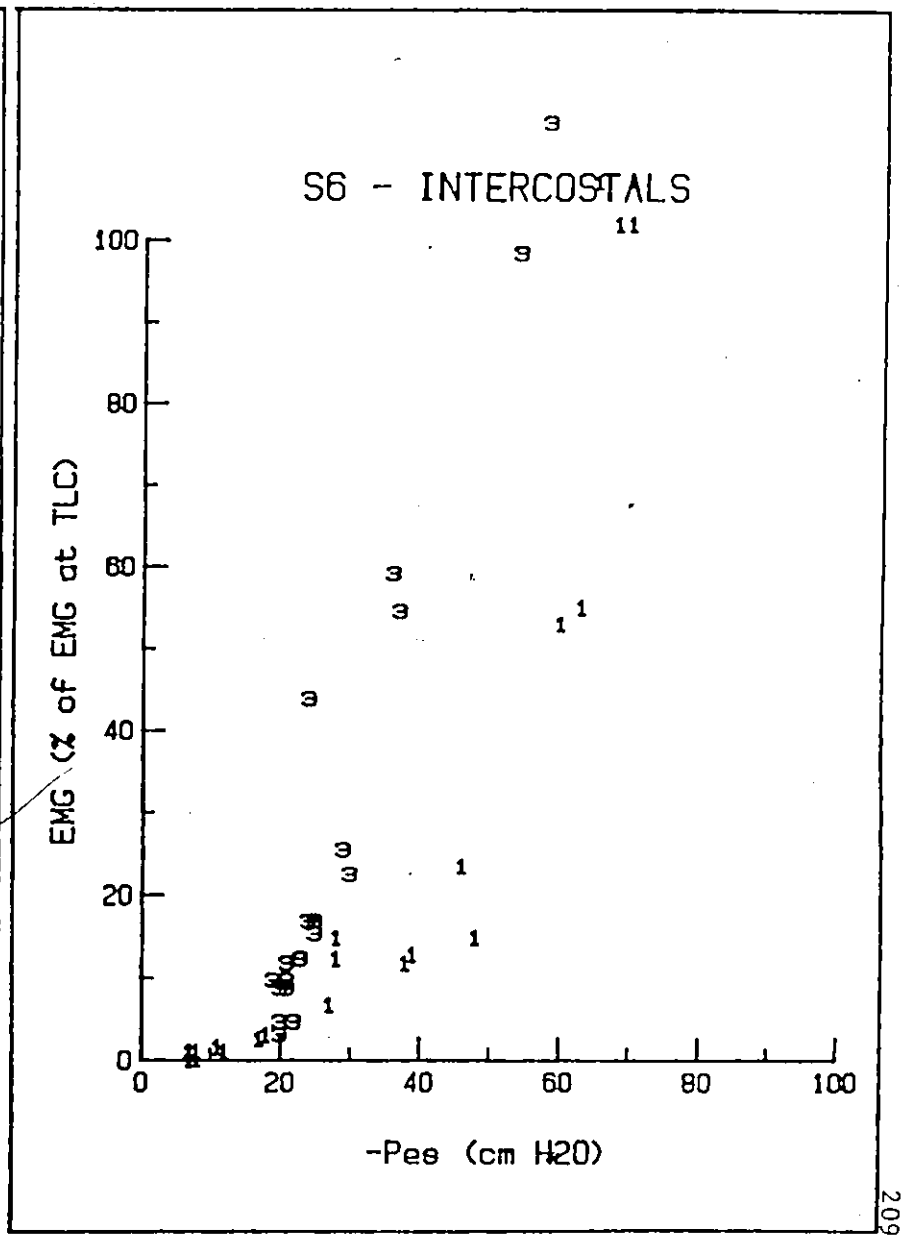

S6 - INTERCOSTALS
EMG (% of EMG at TLC)
-Pes (cm H20)
0
20
40
60
80
100

Figure 10. Rectified intercostal EMG for different esophageal pressures at three lung volumes for subject 6.

Efforts at e.e.p. (symbol E), 2 l above e.e.p. (2), and at inspiratory capacity (symbol T, total lung capacity).

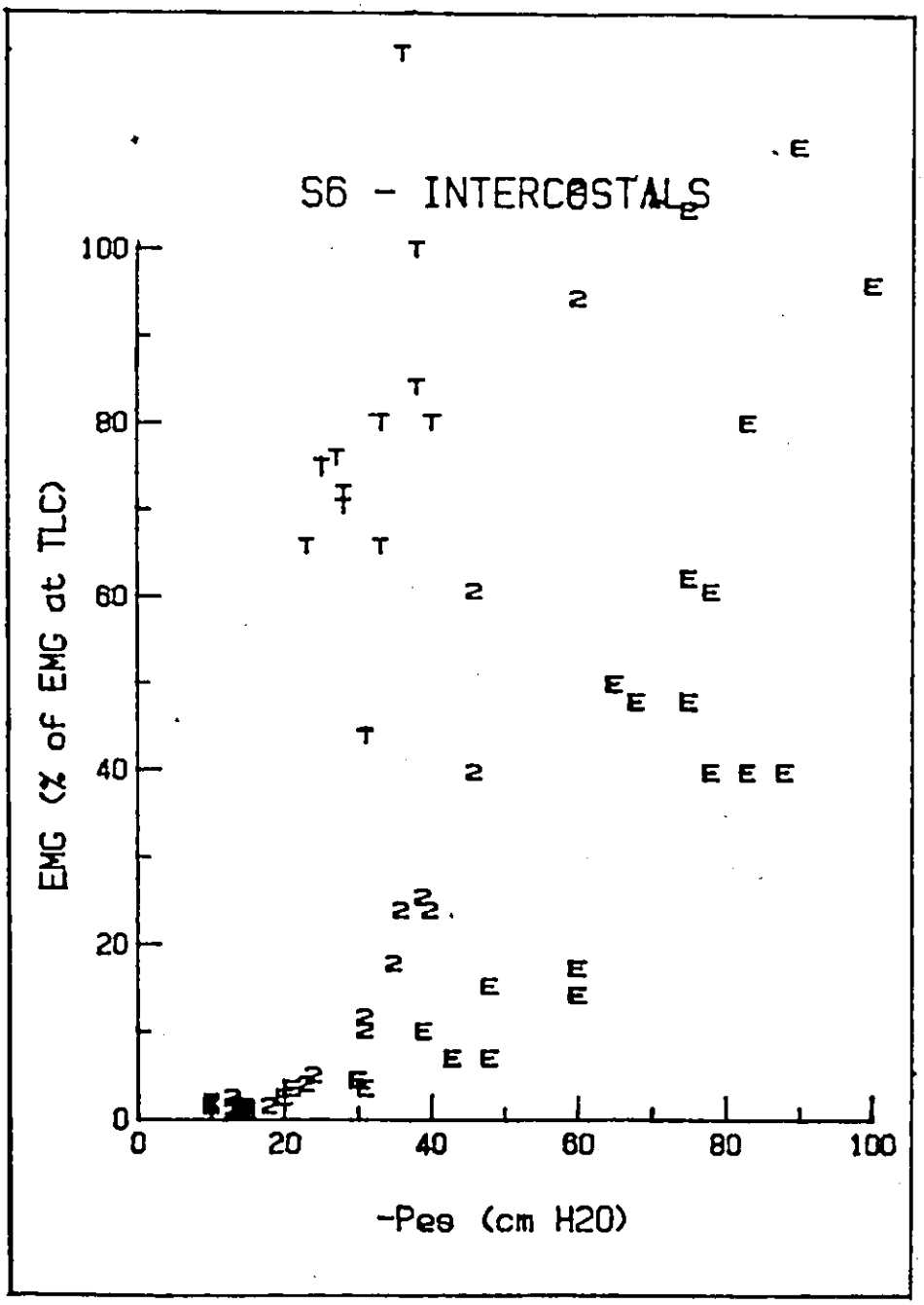
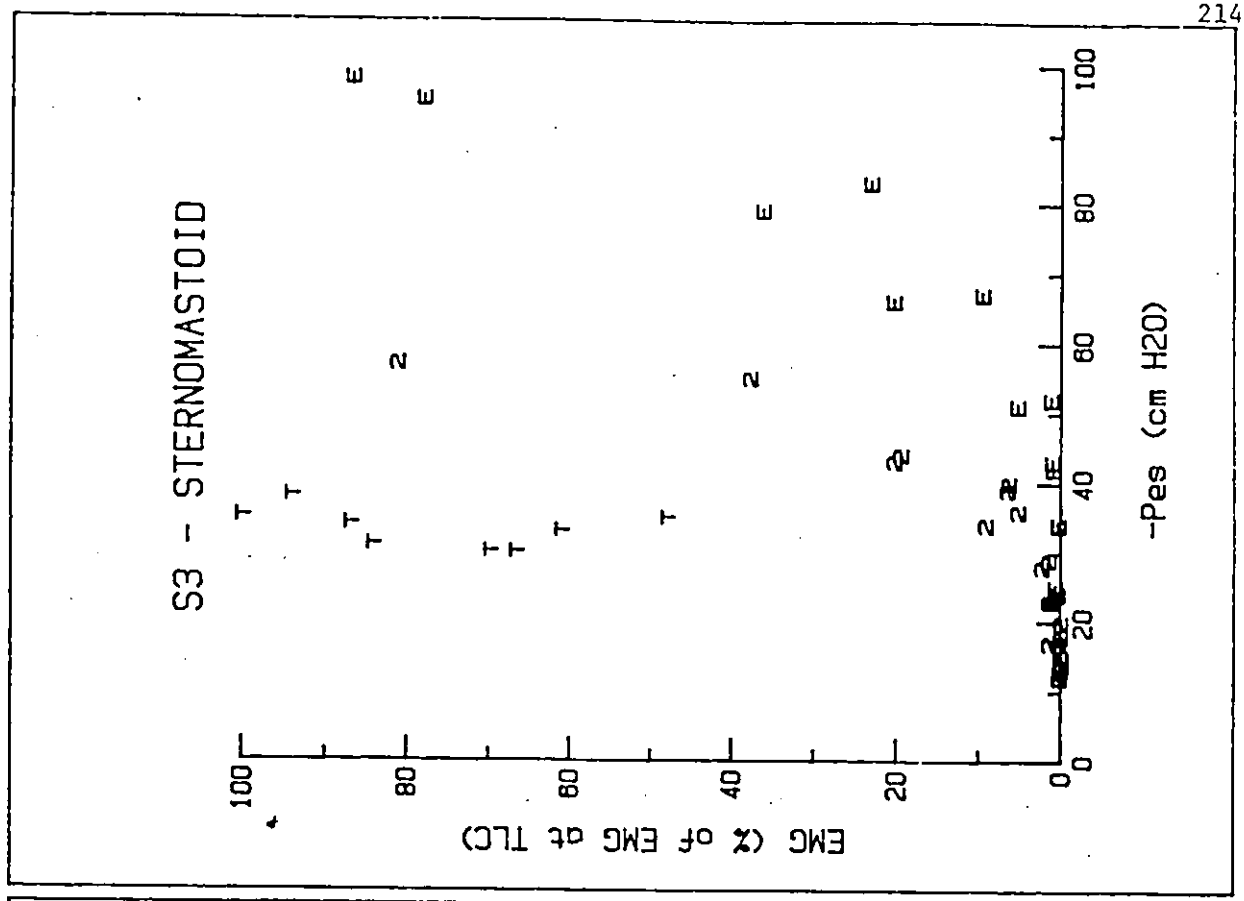

S6 - INTERCOSTALS
EMG (% of EMG at TLC)
-Pes (cm H20)
0
20
40
60
80
100

Figure 11. Rectified scalenes EMG for different esophageal pressures at three lung volumes for subject 3 (pg 214).

Efforts at e.e.p. (symbol E), 2 l above e.e.p. (2), and at inspiratory capacity (T).

Figure 12. Rectified sternomastoid EMG for different esophageal pressures at three lung volumes for subject 3.

Efforts at e.e.p. (symbol E), 2 l above e.e.p. (2), and at inspiratory capacity (T).


S3 - STERNOMASTOID
EMG (% of EMG at TLC)
-Pes (cm H2O)
0
20
40
60
80
100

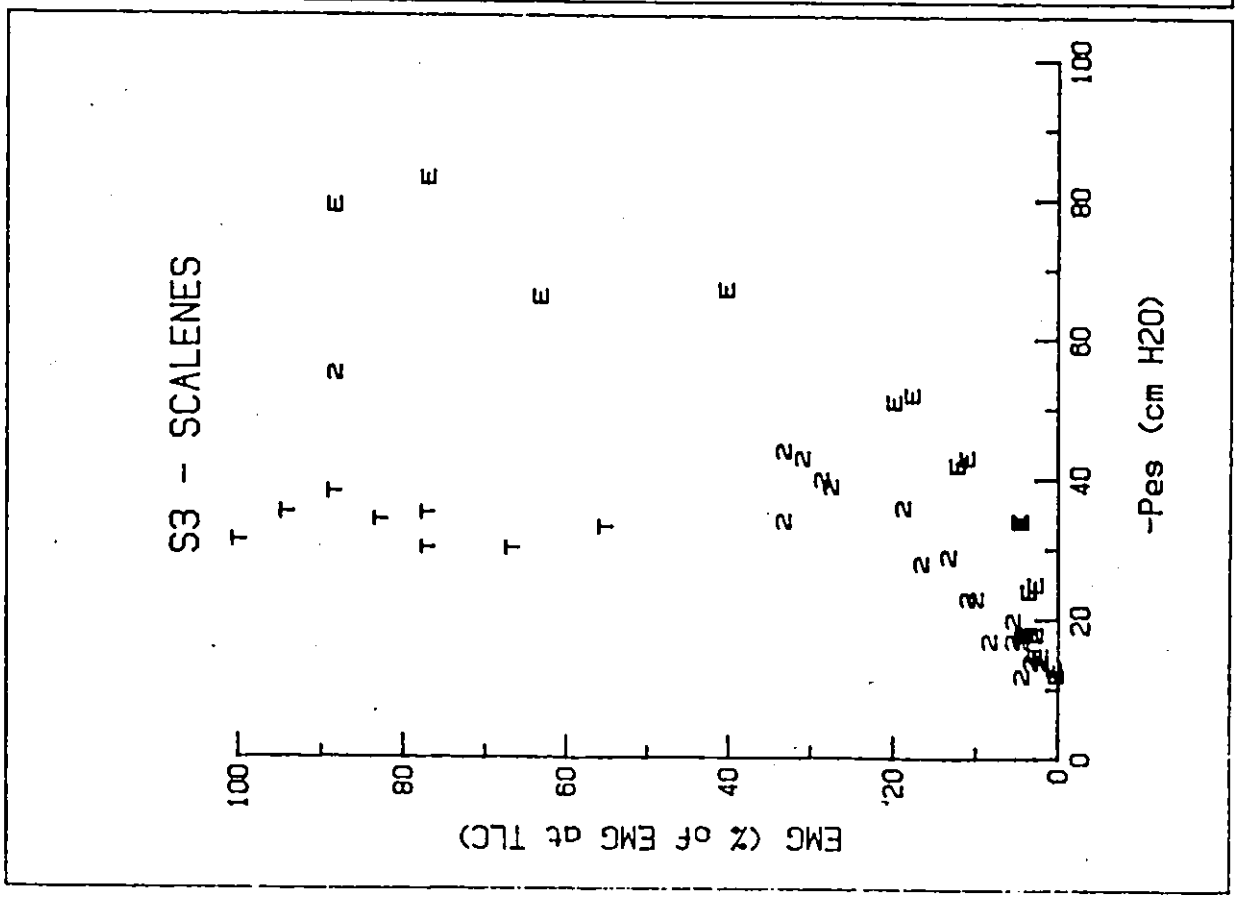

S3 - SCALENES
EMG (% of EMG at TLC)
-Pes (cm H2O)
0
20
40
60
80
100

Figure 13. Rectified sternomastoid EMG for different esophageal pressures at three lung volumes for subject 6.

Efforts at e.e.p. (symbol E), 2 l above e.e.p. (2), and at inspiratory capacity (T).

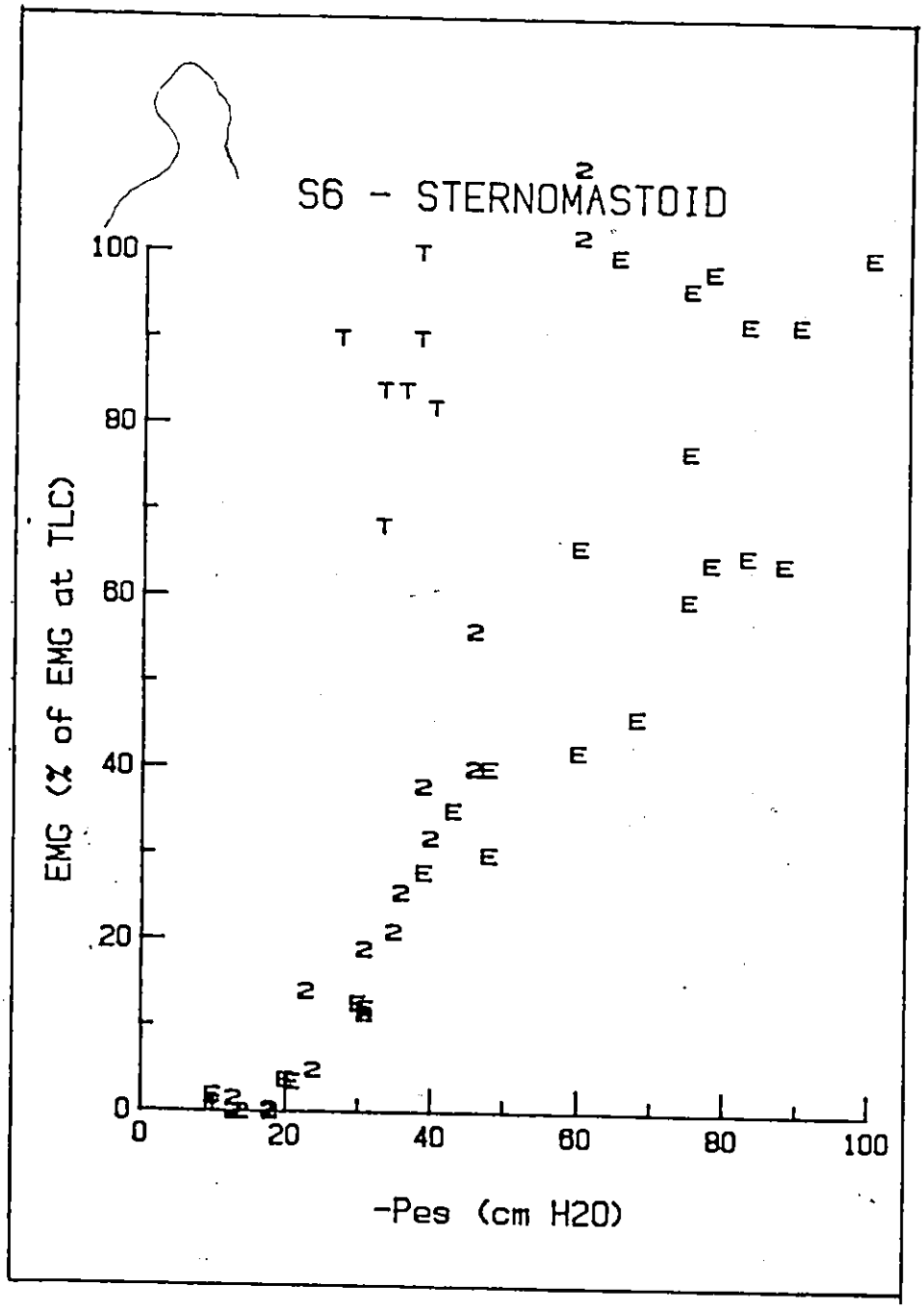

S6 - STERNOMASTOID
EMG (% of EMG at TLC)
-Pes (cm H2O)
0
20
40
60
80
100

Figure 14. Rectified sternomastoid EMG for different esophageal pressures at two lung volumes for subject 6.

Efforts at 1 l (symbol 1) and 3 l (3) above e.e.p.

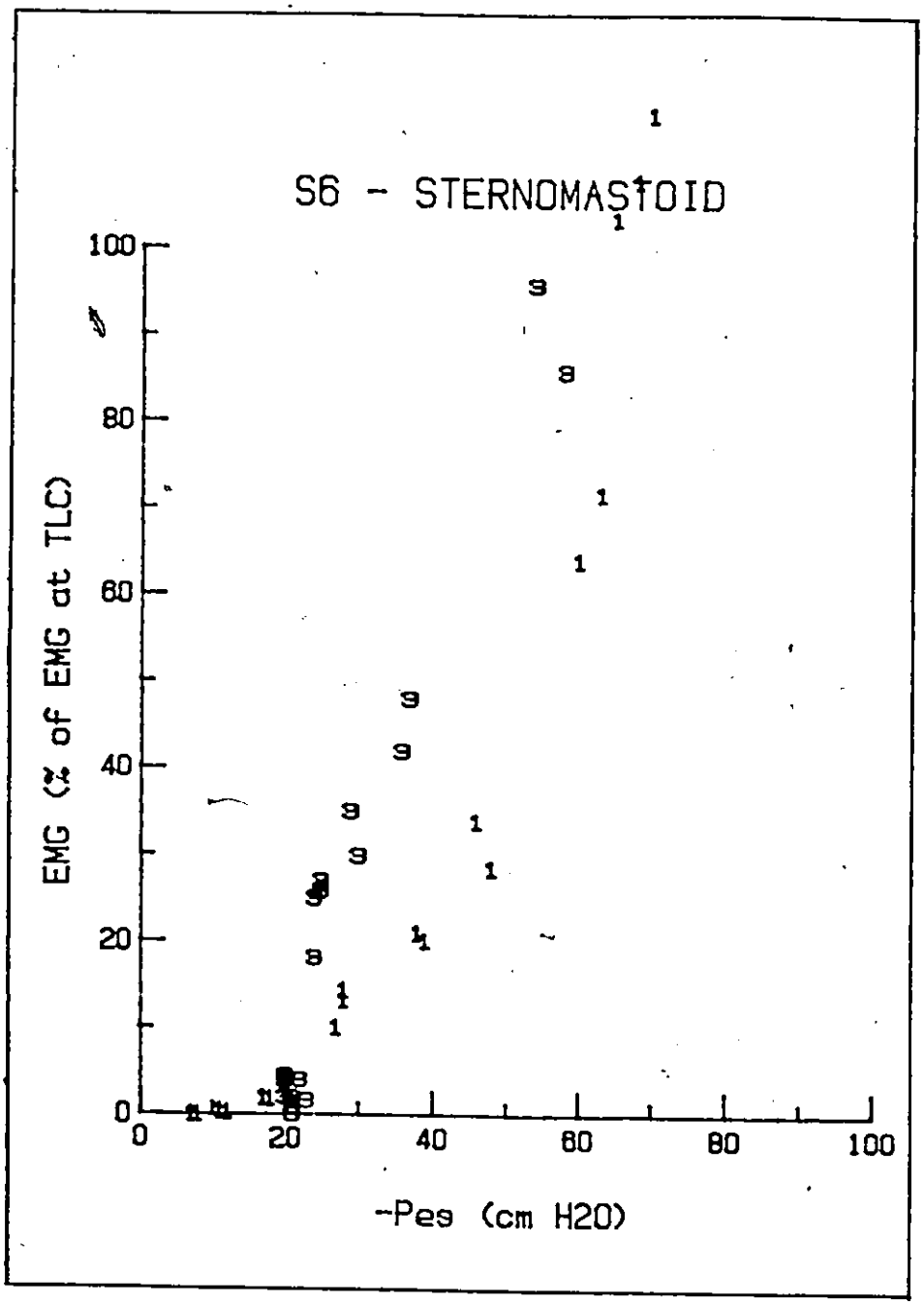

S6 - STERNOMASTOID
EMG (% of EMG at TLC)
100
80
60
40
20
0
0
20
40
60
80
100
-Pes (cm H2O)

Figure 15. Rectified scalenes EMG for different esophageal pressures at five lung volumes for subject 3.

Efforts at e.e.p. (symbol E), 1 1 (1), 2 1 (2), and 3 1 (3) above e.e.p., and at inspiratory capacity (T).

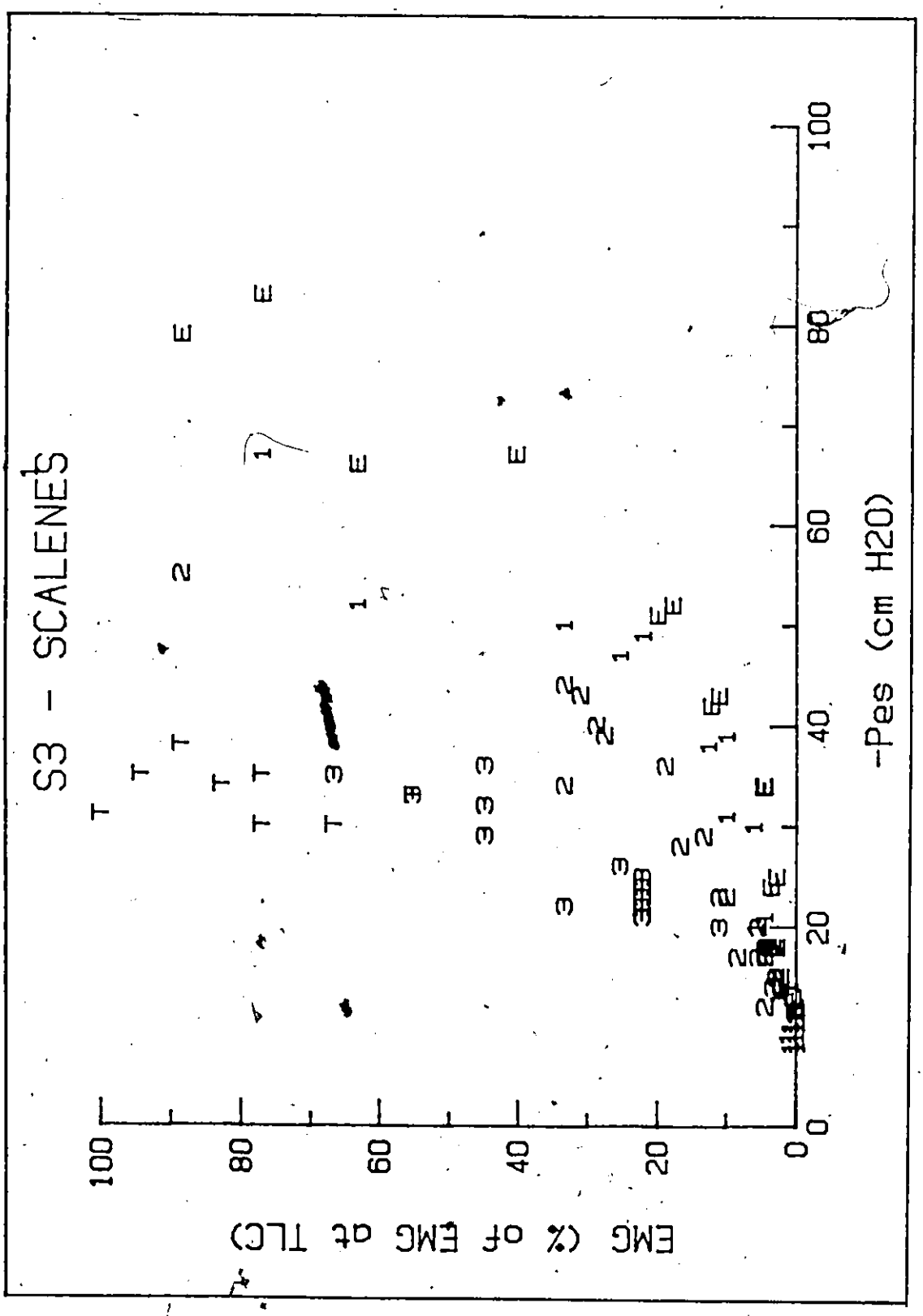

S3 - SCALENES
EMG (% of EMG at TLC)
-Pes (cm H2O)
0
20
40
60
80
100

Figure 16. Rectified scalenes EMG for different inspiratory muscle pressures at five lung volumes for subject 3.

Efforts at e.e.p. (symbol E), 1 l (1), 2 l (2), and 3 l (3) above e.e.p., and at inspiratory capacity (T).

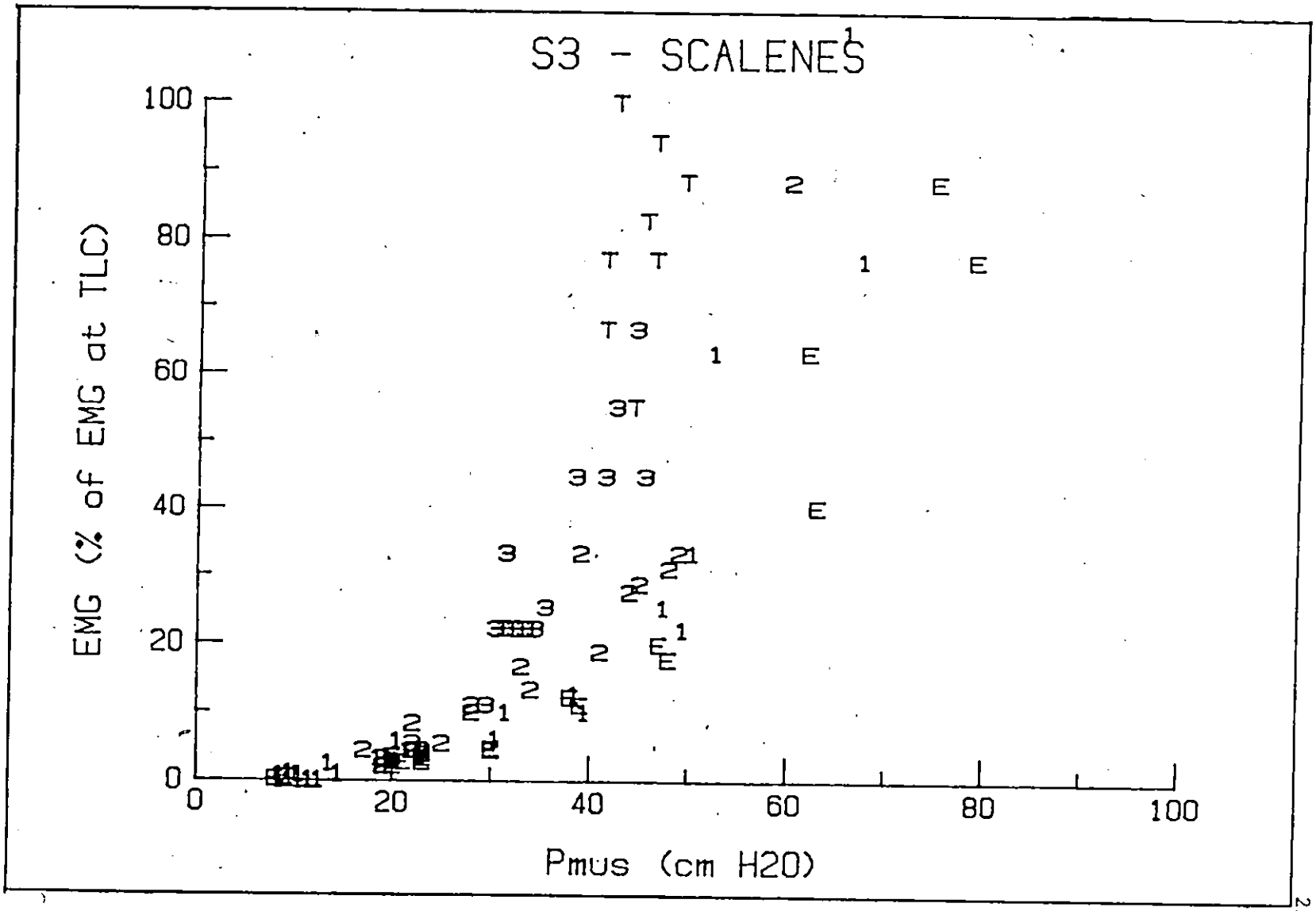
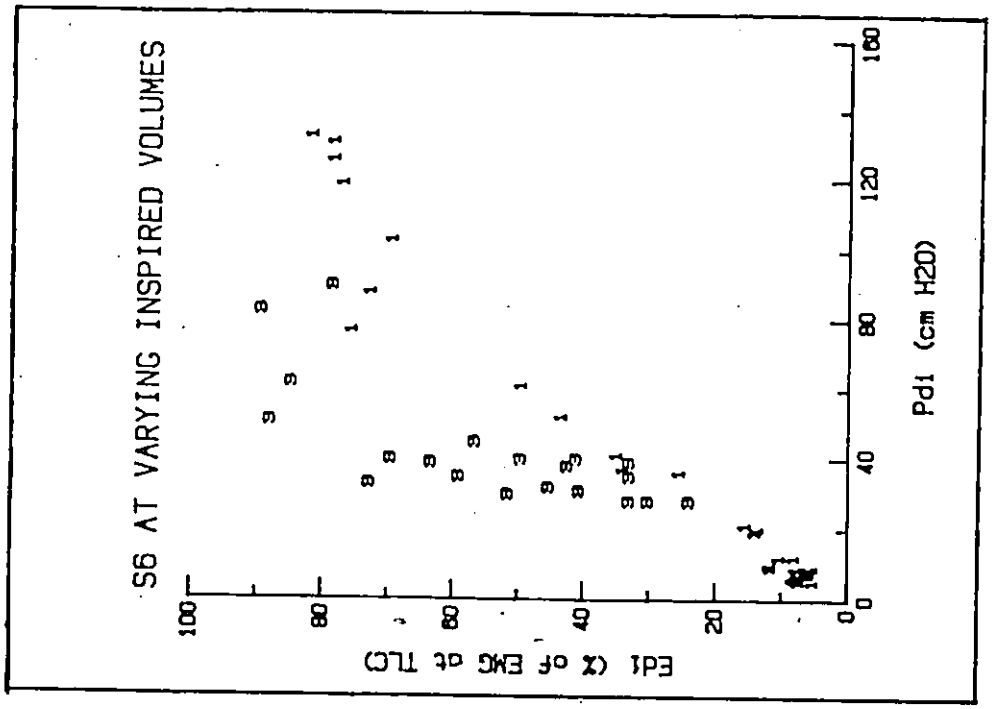

S3 - SCALENES
EMG (% of EMG at TLC)
Pmus (cm H20)
0
20
40
60
80
100

Figure 17. Rectified diaphragm EMG for different esophageal pressures at two lung volumes for subject 6 (pg 225).

Efforts at 1 1 (symbol 1) and 3 1 (3) above e.e.p.

Figure 18. Rectified diaphragm EMG for different transdiaphragmatic pressures at two lung volumes for subject 6. Efforts at 1 l (symbol 1) and 3 l (3) above e.e.p.


S6 AT VARYING INSPIRED VOLUMES
Edi (% of EMG at TLC)
Pdi (cm H2O)
0
20
40
60
80
100
0
40
80
120
160

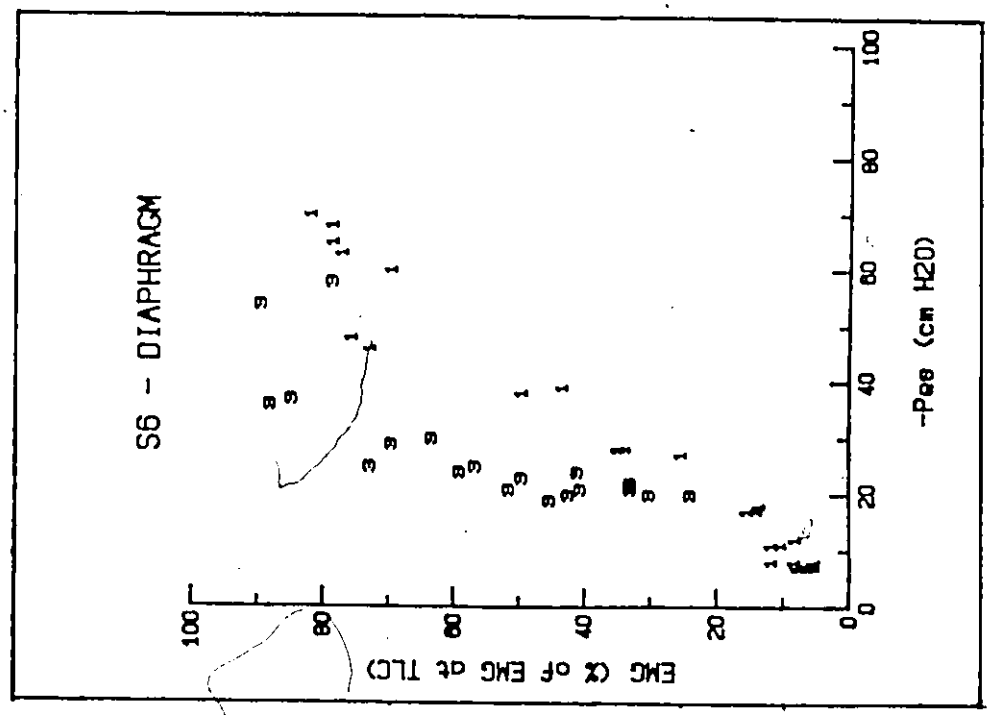

S6 - DIAPHRAGM
EMG (% of EMG at TLC)
-Pes (cm H2O)
0
20
40
60
80
100
0
20
40
60
80
100

Figure 19. Change in respiratory and hand muscle strength of subject 1 with time of curarization.

Graphed as a percentage of the pre-curare level are: inspiratory capacity (symbol ●), maximum inspiratory mouth pressure (▲), hand grip strength (+), and expiratory reserve volume (o). The amount of curare infused (*) is an accumulative proportion of the total dose eventually given.

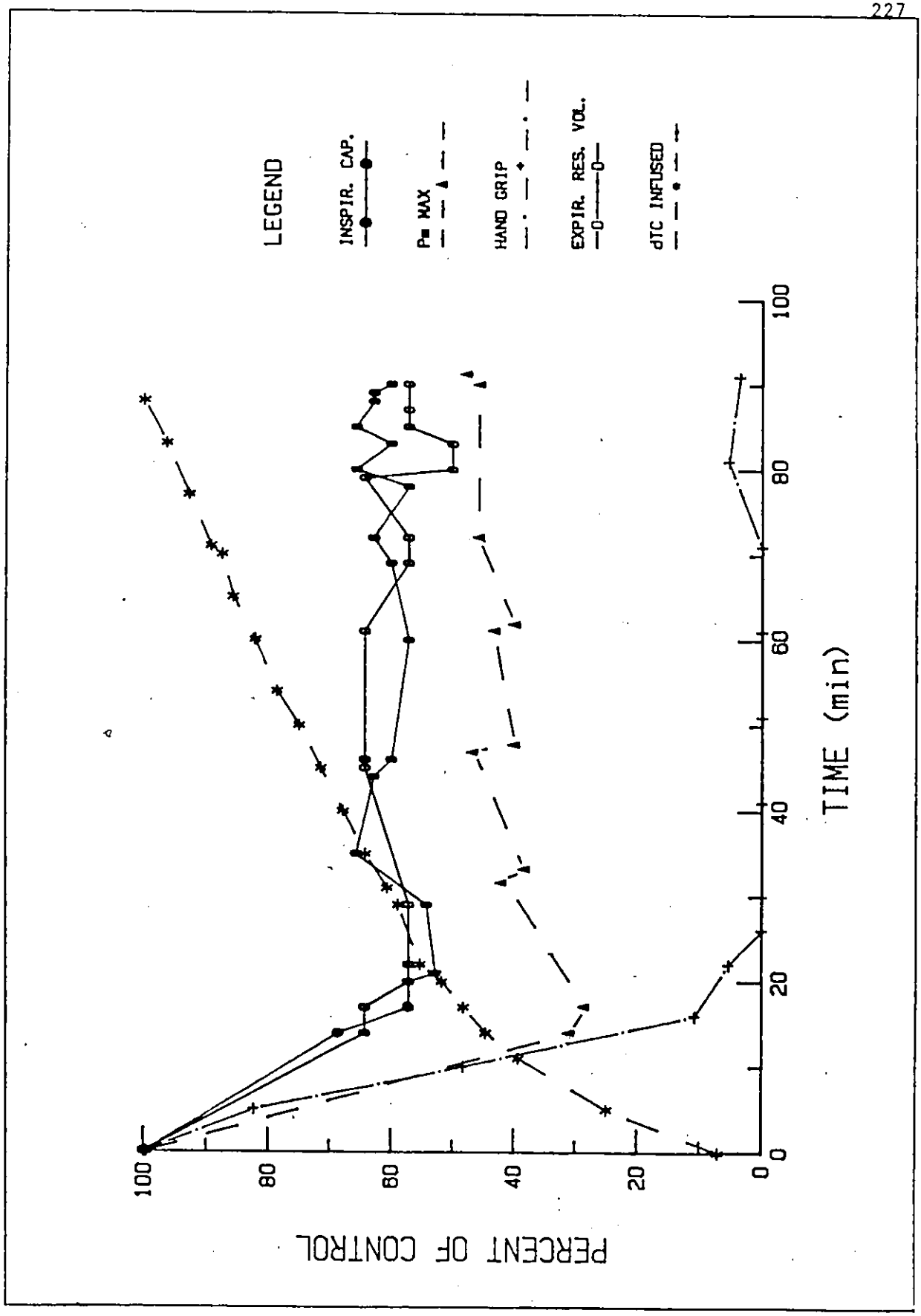

LEGEND
INSPIR. CAP.
Pm MAX
HAND GRIP
EXPIR. RES. VOL.
dTC INFUSED
PERCENT OF CONTROL
TIME (min)
0
20
40
60
80
100

Figure 20. Inspiratory capacity of subject 4 with time of curarization.

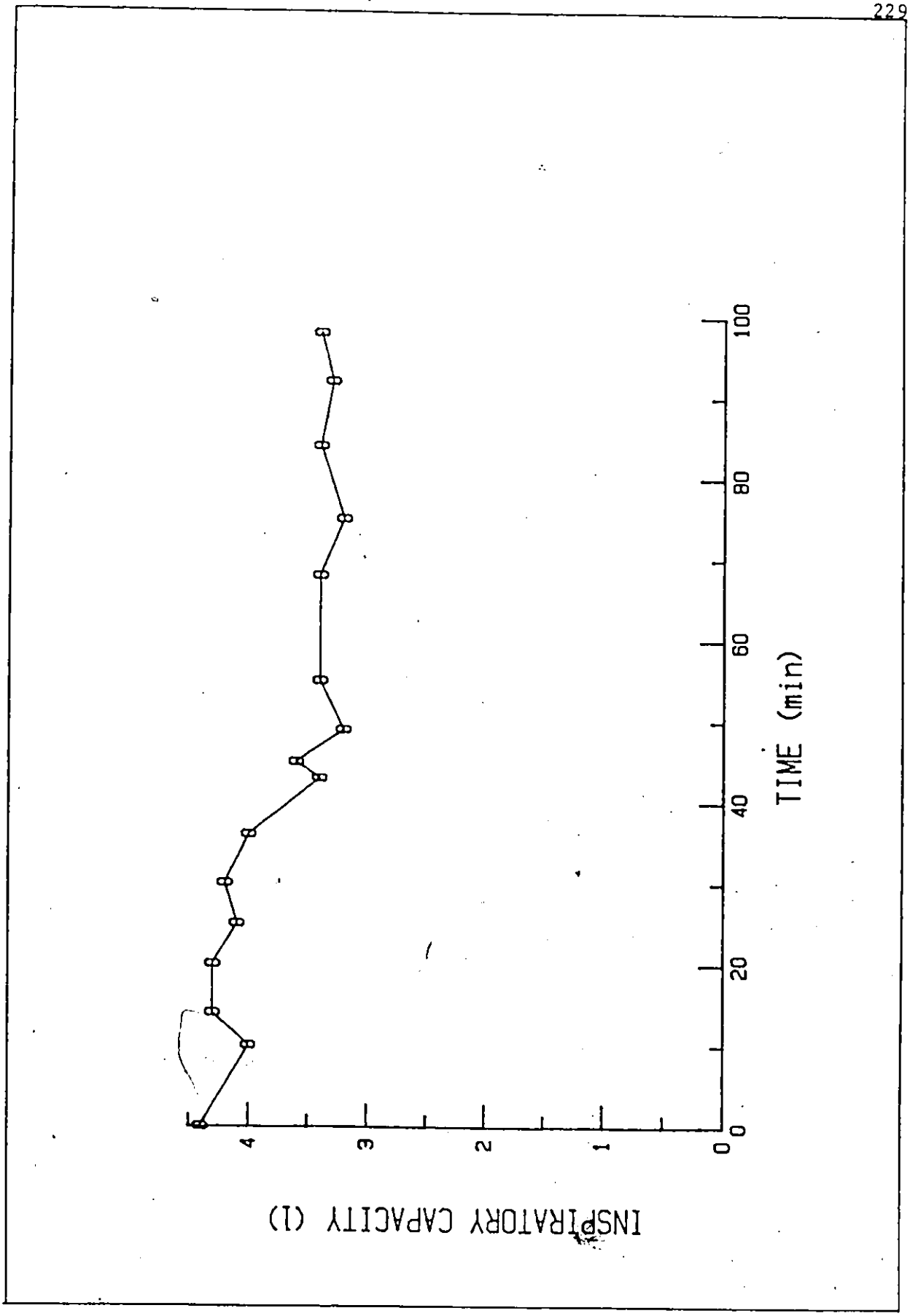

INSPIRATORY CAPACITY (l)
0
1
2
3
4
0
20
40
60
80
100
TIME (min)

Figure 21. Inspiratory capacity of subject 5 with time of curarization.

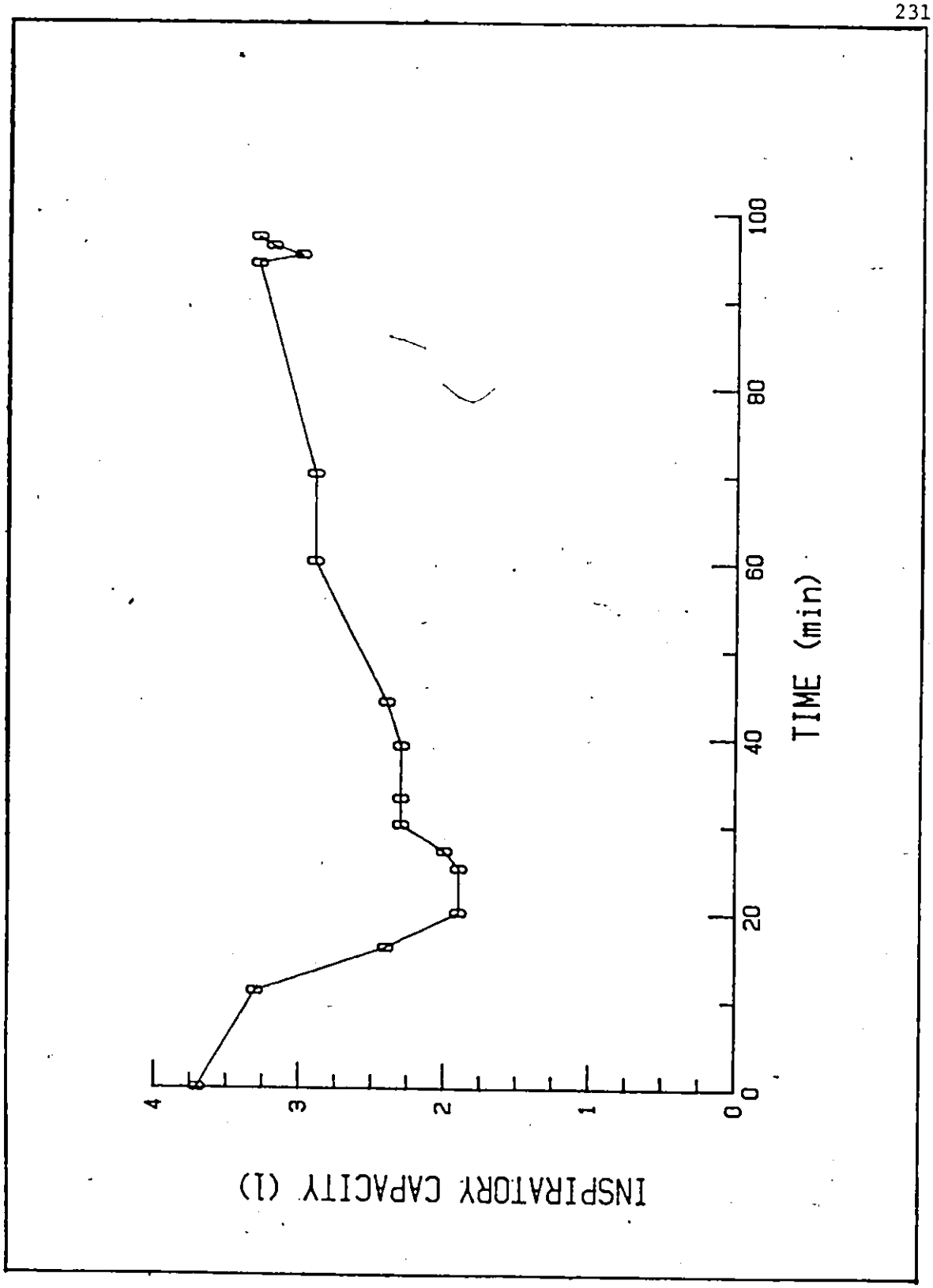
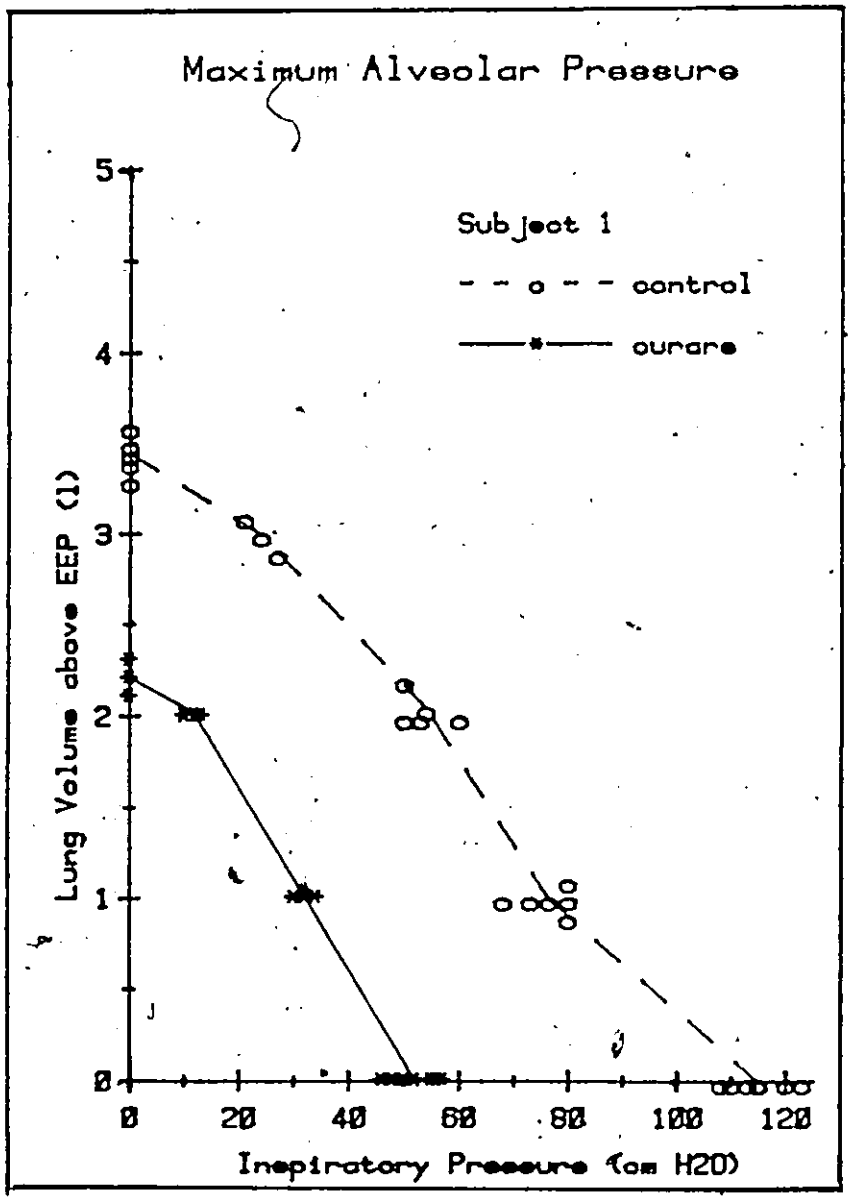

INSPIRATORY CAPACITY (l)
0
1
2
3
4
TIME (min)
0
20
40
60
80
100

Figure 22. Maximum inspiratory alveolar pressure over inspiratory capacity range before (symbol o) and during (*) curarization in subject 1 (pg 234).

Figure 23. Maximum inspiratory alveolar pressure over inspiratory capacity range before (symbol o) and during (*) curarization in subject 3.


Maximum Alveolar Pressure
Subject 1
- - o - - control
——*—— curare
Lung Volume above EEP (l)
0
1
2
3
4
5
0
20
40
60
80
100
120
Inspiratory Pressure (cm H2O)

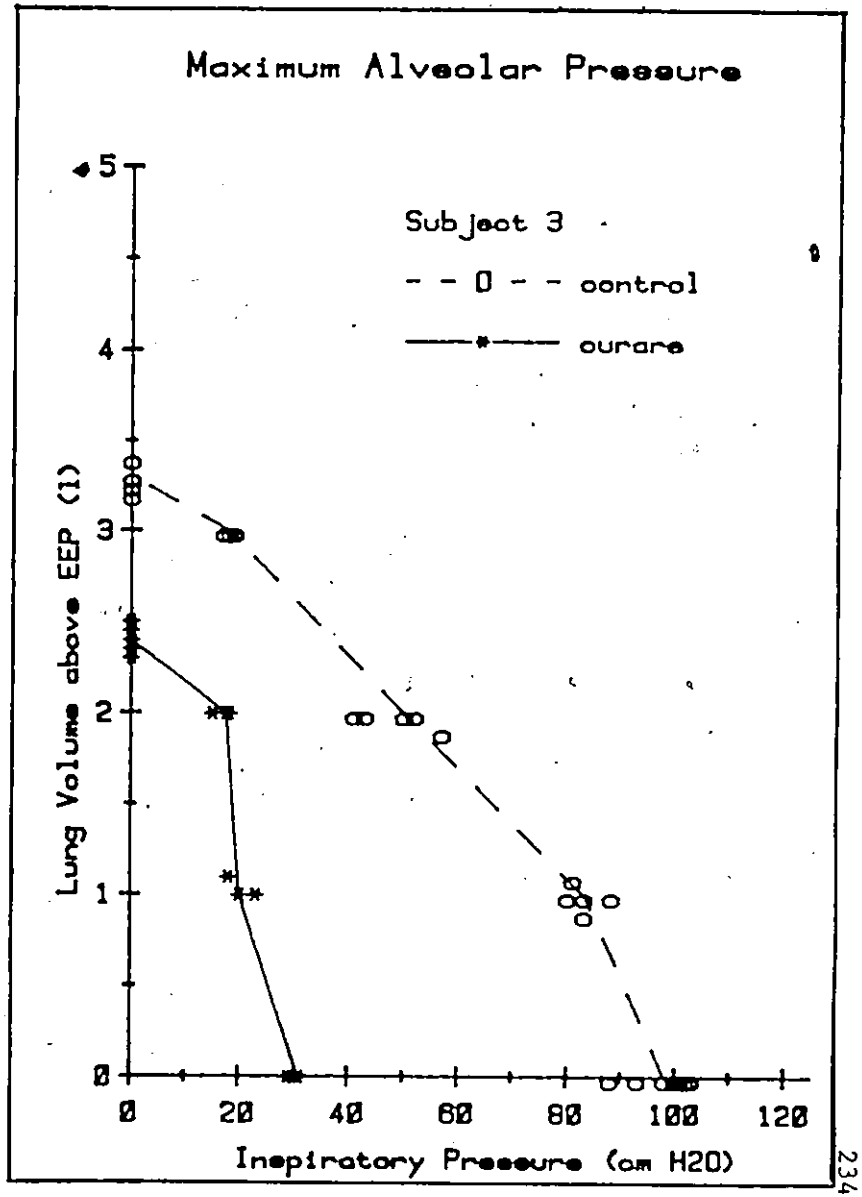

Maximum Alveolar Pressure
Subject 3
- - □ - - control
——*—— curare
Lung Volume above EEP (l)
0
1
2
3
4
5
0
20
40
60
80
100
120
Inspiratory Pressure (cm H2O)

Figure 24. Static alveolar pressure-lung volume curve of respiratory system before (symbol o) and during (*) curarization in subject 5.

Volume is referenced to the end-expiratory position.

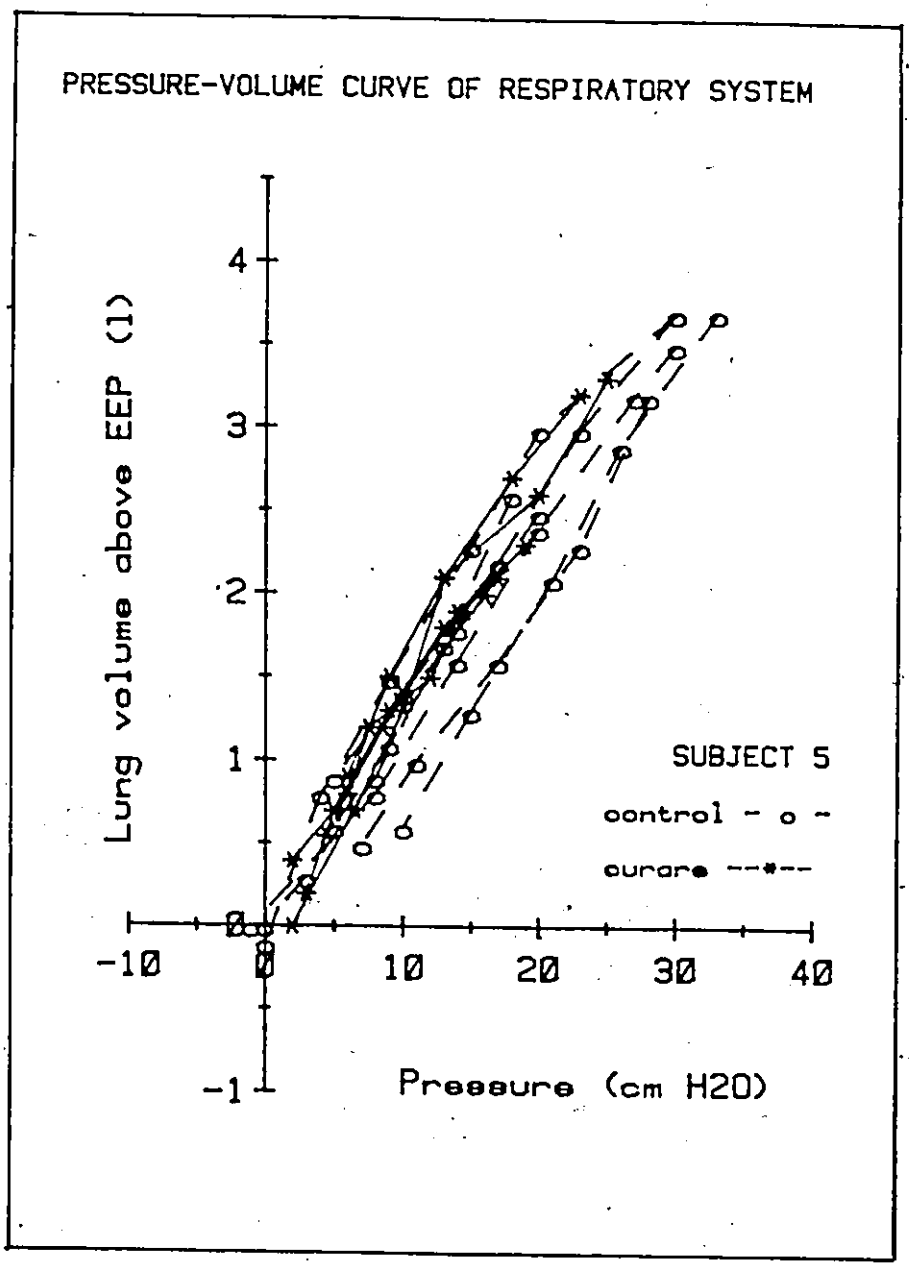

PRESSURE-VOLUME CURVE OF RESPIRATORY SYSTEM
Lung volume above EEP (l)
4
3
2
1
0
-1
-10
0
10
20
30
40
Pressure (cm H20)
SUBJECT 5
control - o -
curare --*--

Figure 25. Static pressure-volume curve of lung before (symbol o) and during (*) curarization in subject 1.

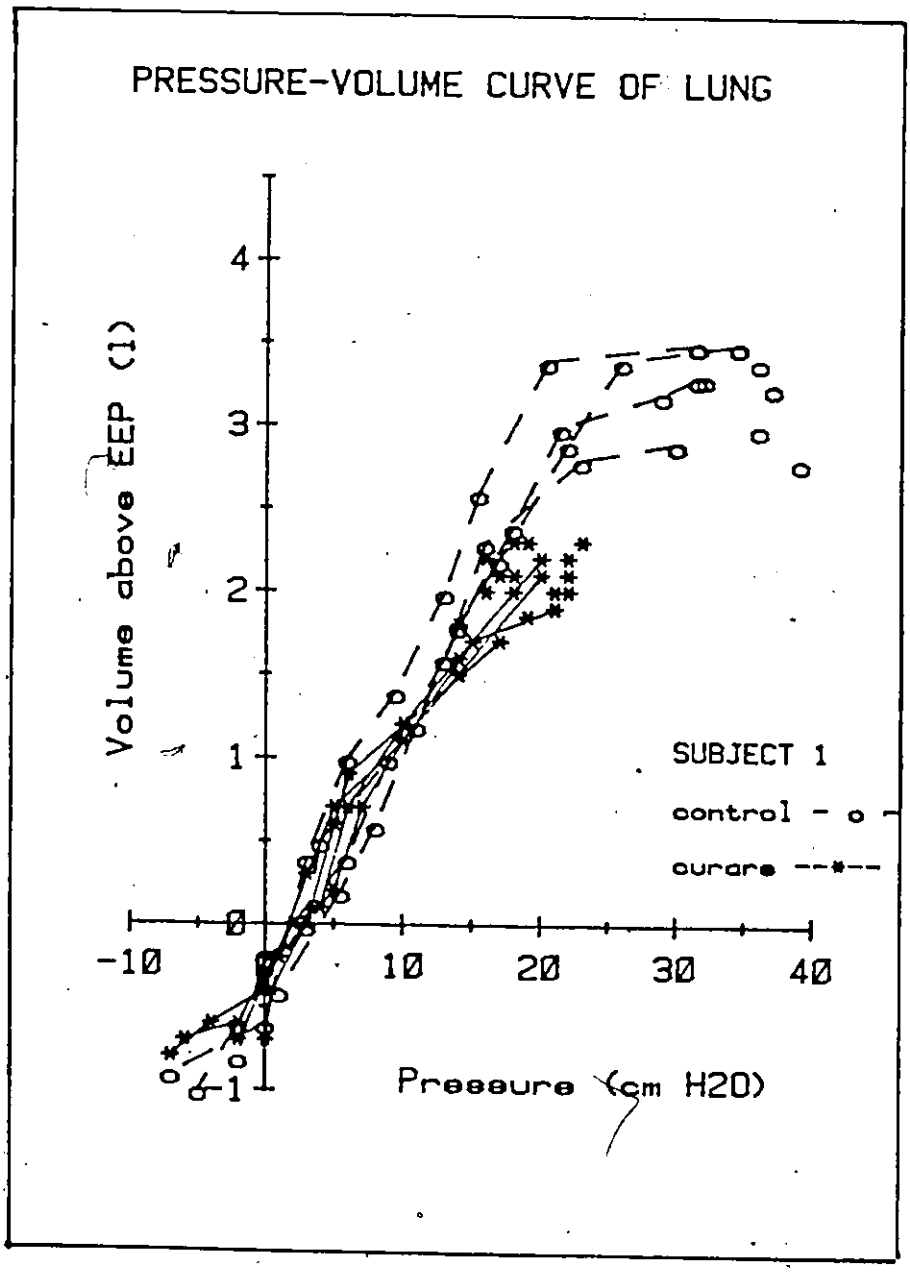

PRESSURE-VOLUME CURVE OF LUNG
Volume above FEP (l)
4
3
2
1
0
-1
-10
10
20
30
40
Pressure (cm H20)
SUBJECT 1
control - o
curare --*--

Figure 26. Static pressure-volume curve of chest wall before (symbol o) and during (*) curarization in subject 4.

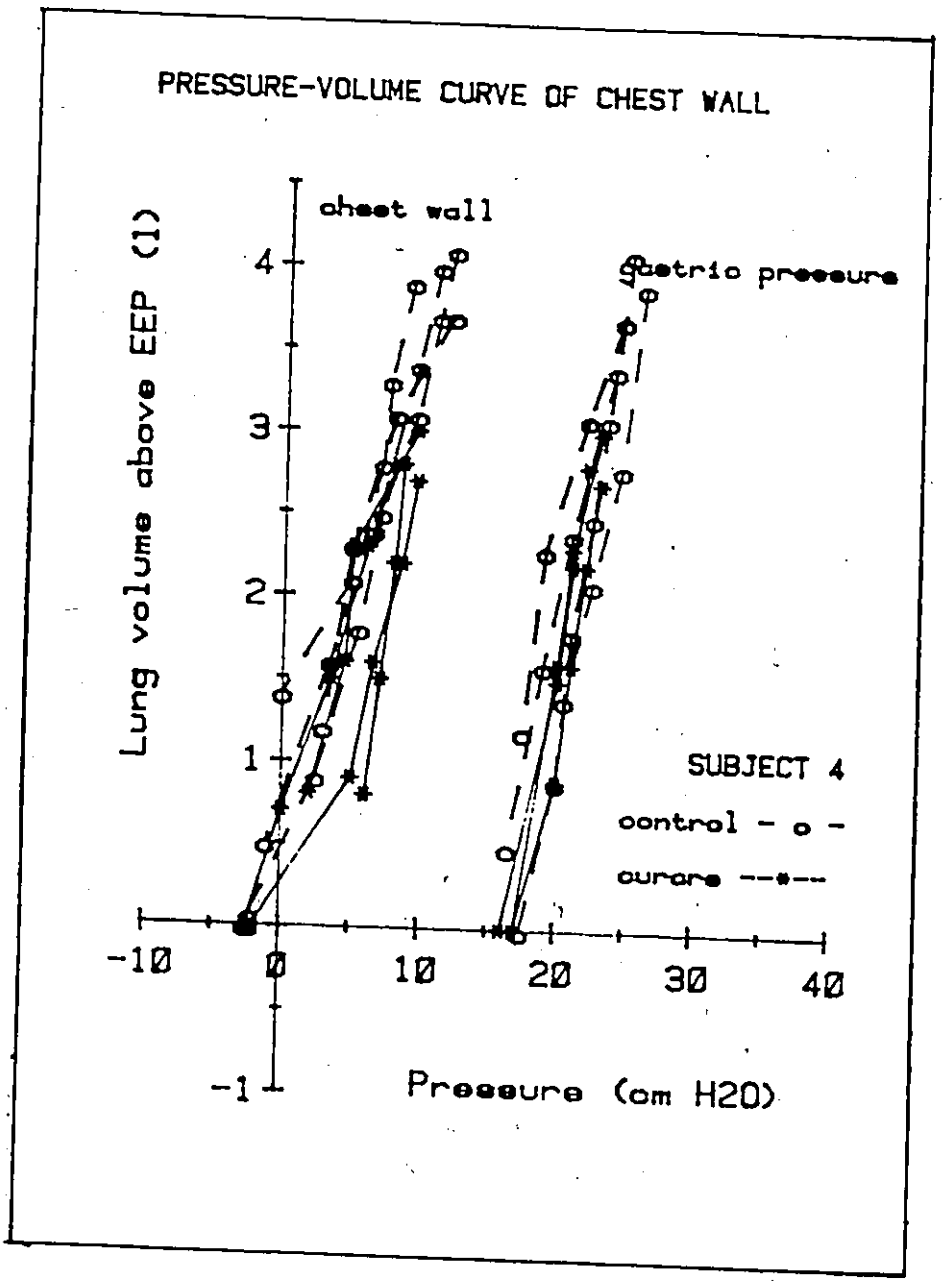
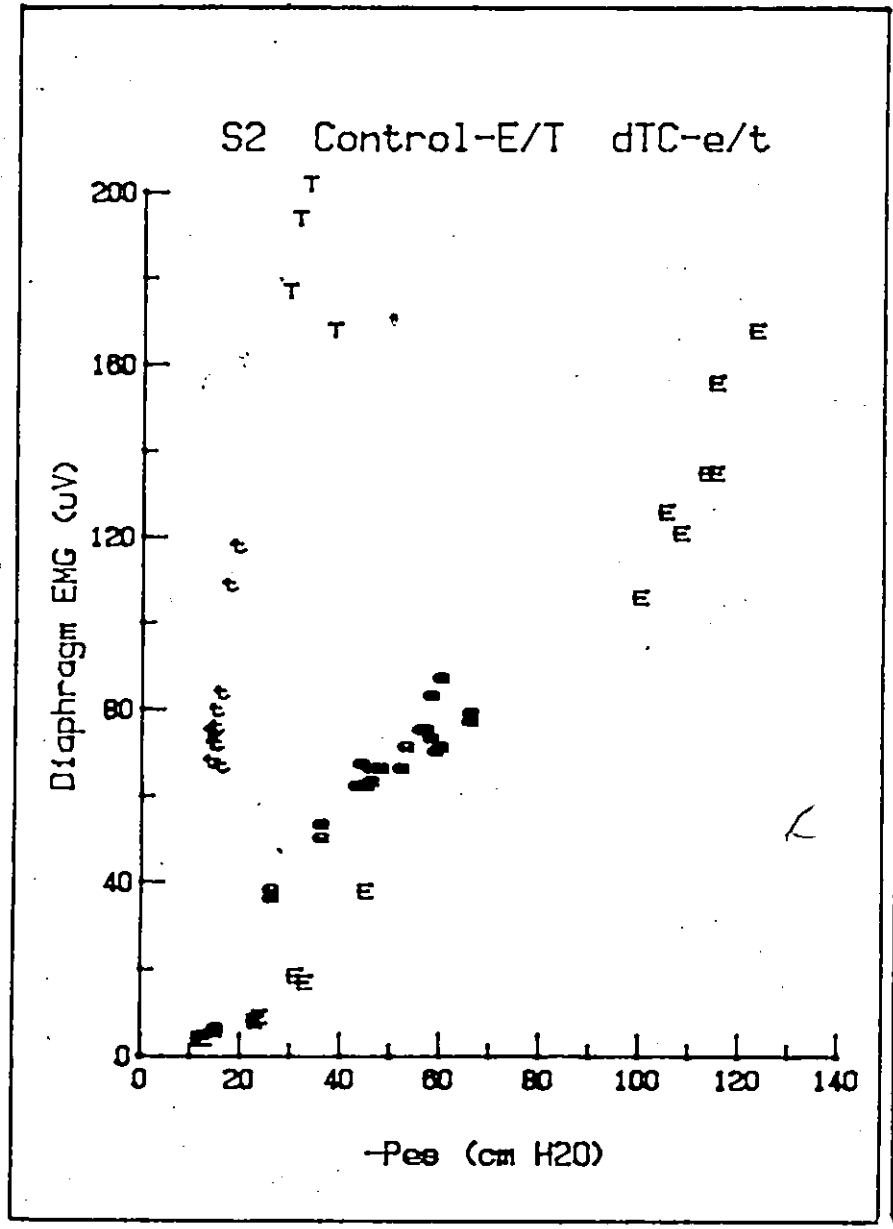

PRESSURE-VOLUME CURVE OF CHEST WALL
chest wall
gastric pressure
Lung volume above EEP (l)
4
3
2
1
-1
-10
0
10
20
30
40
SUBJECT 4
control - o -
curare --*--
Pressure (cm H2O)

Figure 27. Rectified diaphragm EMG for different esophageal pressures in subject 2 before and during curarization.

Figure 27a. Efforts at end-expiratory position before curare (symbol E), at end-expiratory position after curare (symbol e), at total lung capacity before curare (symbol T), and at total lung capacity after curare (t). Figure 27b. Efforts at 1 l above e.e.p. before curare (symbol 1), at 1 l above e.e.p. after curare (o), at 2 l above e.e.p. before curare (2), and at 2 l above e.e.p. after curare (*).


S2 Control-E/T dTC-e/t
Diaphragm EMG (uV)
-Pes (cm H20)
0
40
80
120
160
200
0
20
40
60
80
100
120
140

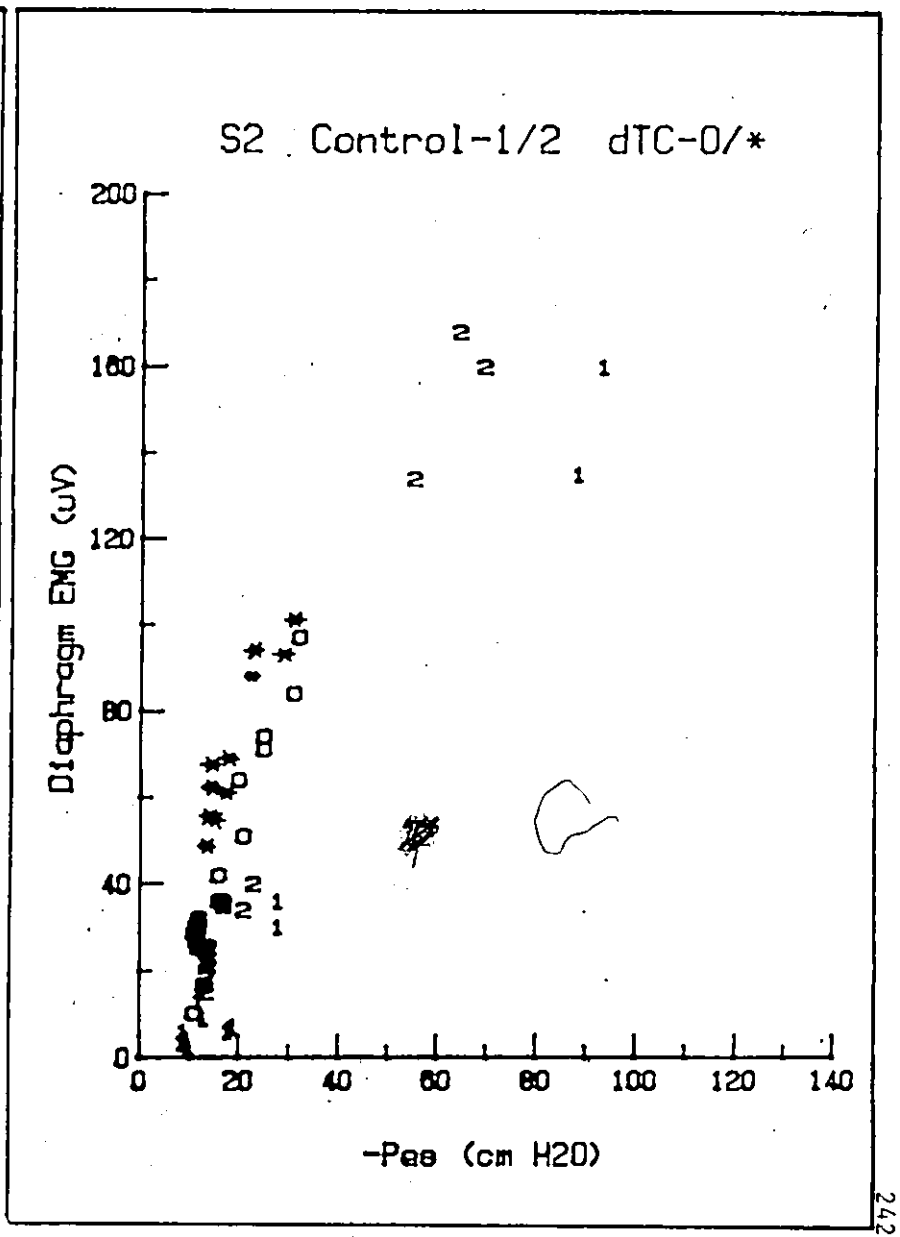

S2 Control-1/2 dTC-0/*
Diaphragm EMG (uV)
-Pes (cm H20)
0
40
80
120
160
200
0
20
40
60
80
100
120
140

Figure 28. Rectified sternomastoid EMG for different esophageal pressures at two lung volumes in subject 5 before and during curarization.

Efforts at 1 l above e.e.p. before curare (symbol l), at 1 l above e.e.p. after curare (o), at 2 l above e.e.p. before curare (2), and at 2 l above e.e.p. after curare (*).

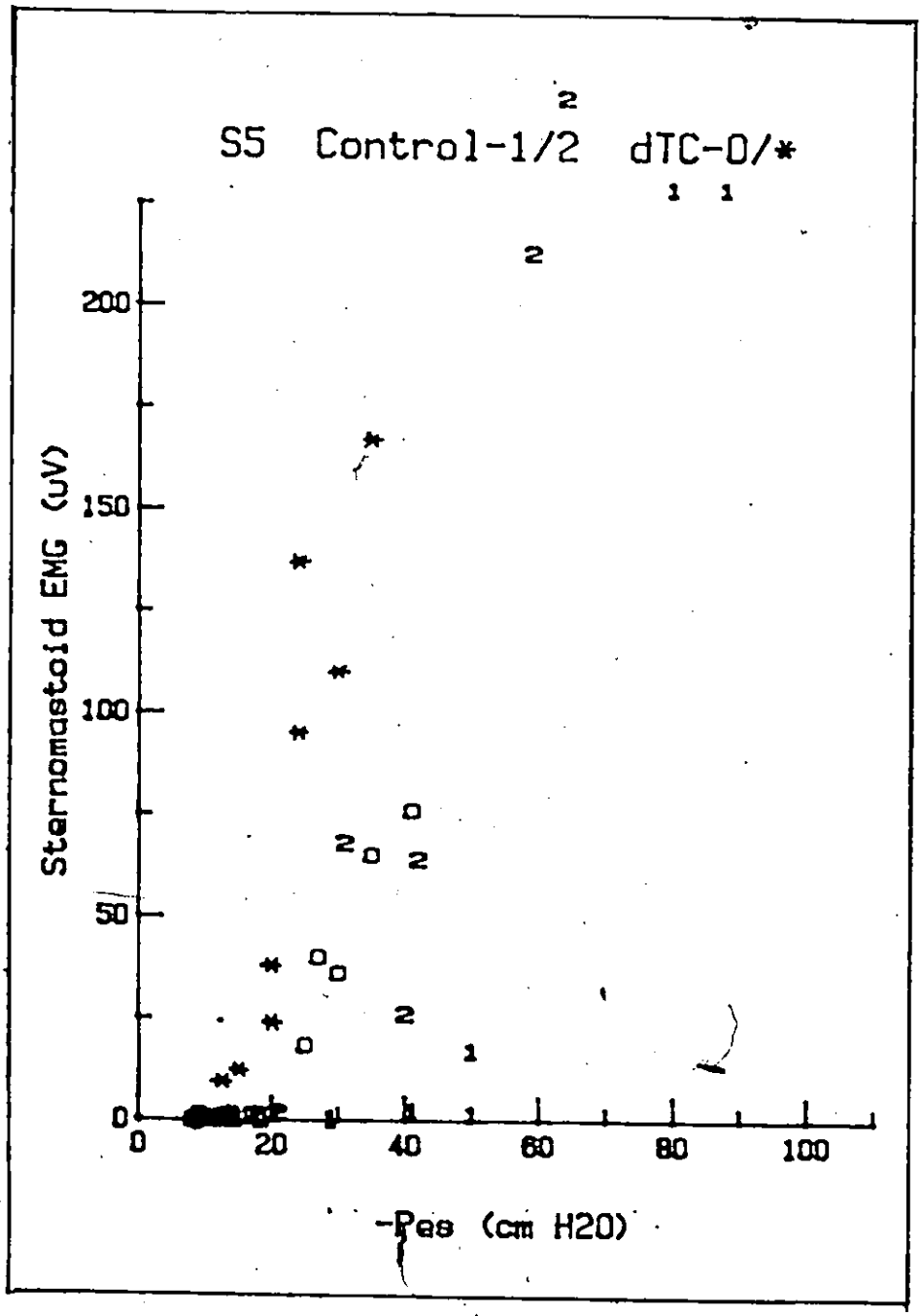

S5 Control-1/2 dTC-O/*
Sternomastoid EMG (uV)
200
150
100
50
0
0
20
40
60
80
100
-Pes (cm H20)

Figure 29. Rectified intercostal EMG for different esophageal pressures at two lung volumes in subject 1 before and during curarization.

Efforts at 1 l above e.e.p. before curare (symbol 1), at 1 l above e.e.p. after curare (o), at 2 l above e.e.p. before curare (2), and at 2 l above e.e.p. after curare (*).

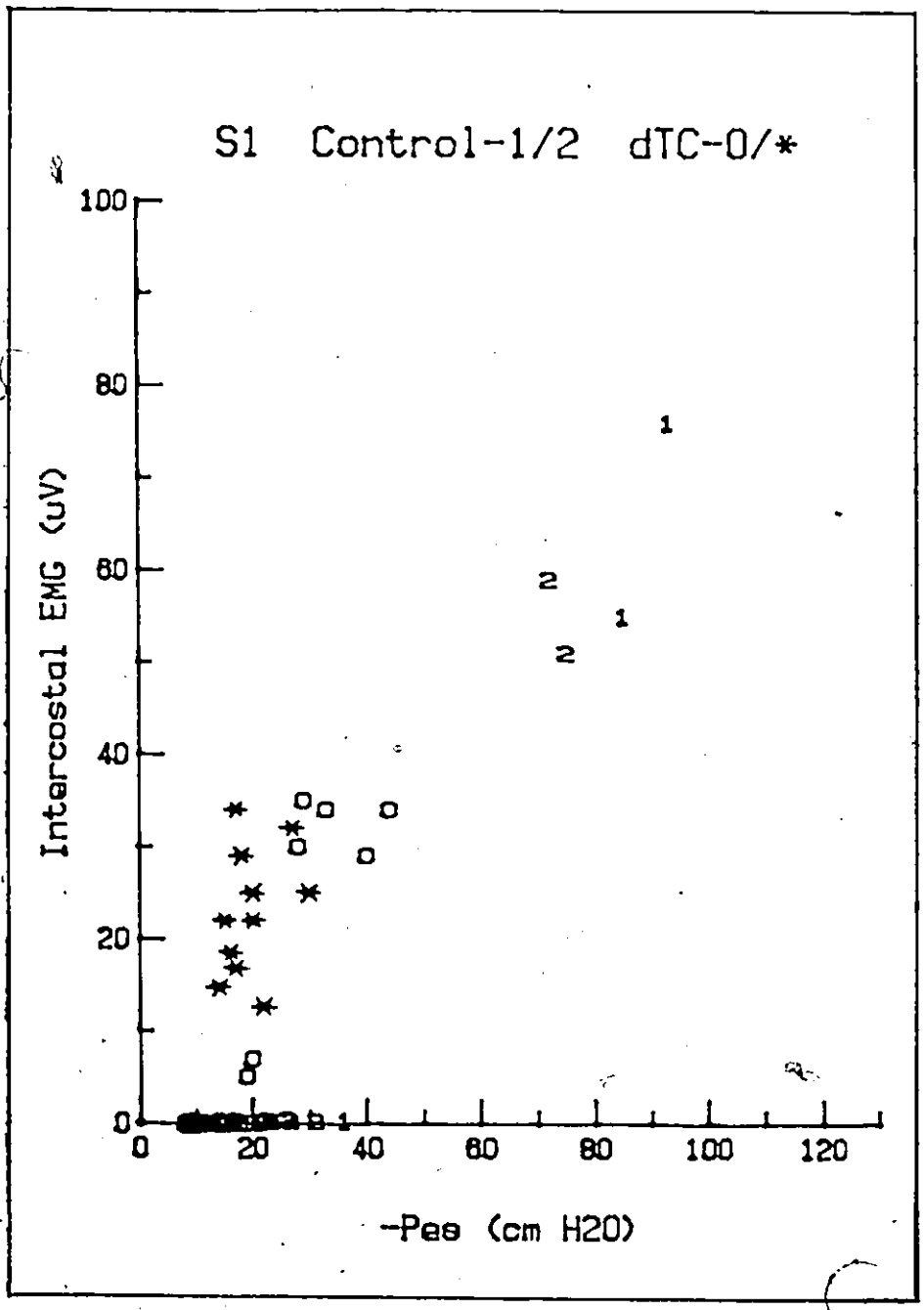

S1 Control-1/2 dTC-0/*
Intercostal EMG (uV)
100
80
60
40
20
0
0
20
40
60
80
100
120
-Pes (cm H20)

Figure 30. Rectified sternomastoid EMG for different esophageal pressures at two lung volumes in subject 3 before and during curarization.

Efforts at 1 l above e.e.p. before curare (symbol 1), at 1 l above e.e.p. after curare (o), at 2 l above e.e.p. before curare (2), and at 2 l above e.e.p. after curare (*).

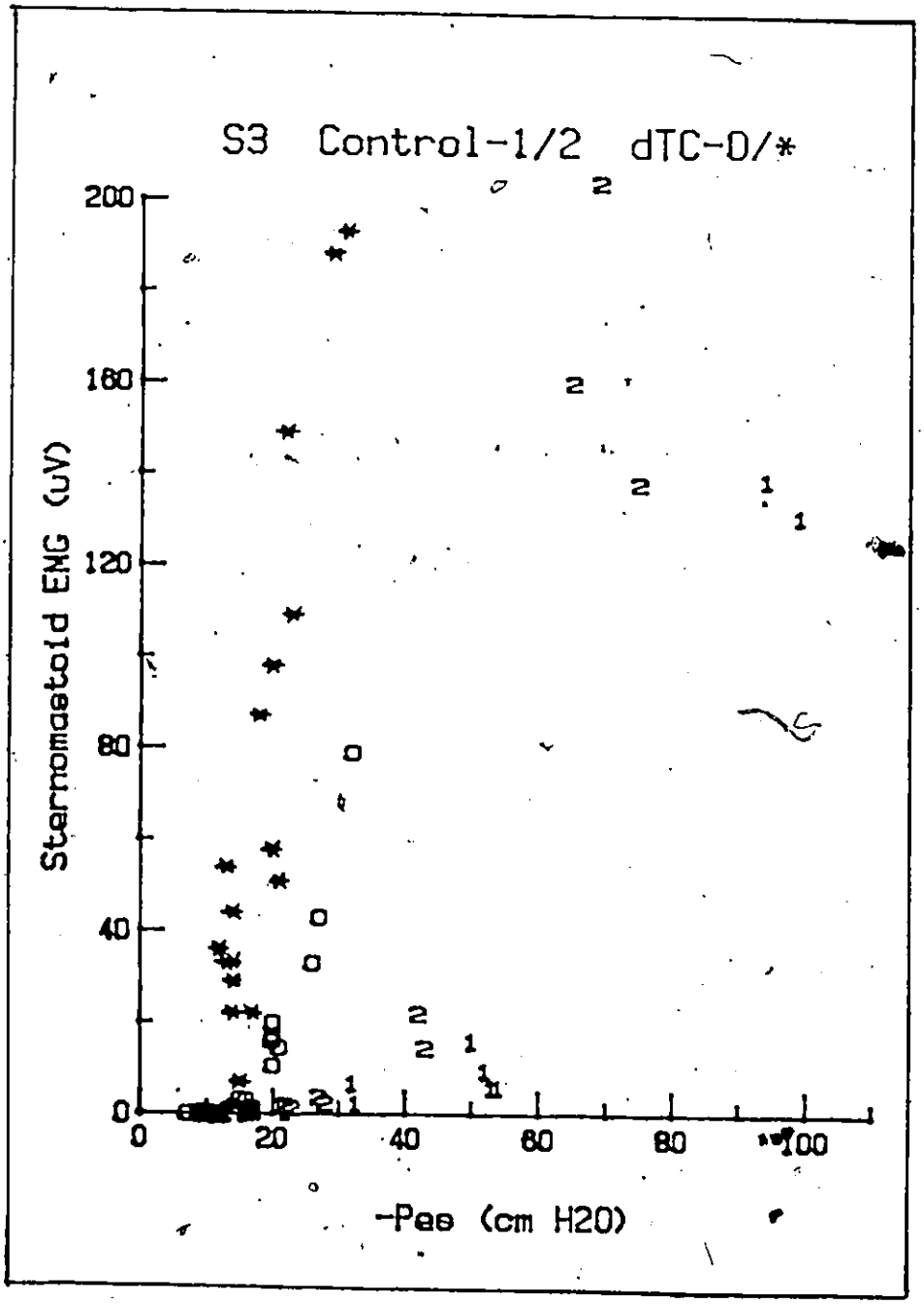

S3 Control-1/2 dTC-D/*
Sternomastoid EMG (uV)
200
160
120
80
40
0
0
20
40
60
80
100
-Pes (cm H20)

Figure 31. Maximum rectified EMG and respiratory muscle pressure during curarization compared to control at four lung volumes in subject 1.

Symbols represent muscle pressure (P), and EMG for diaphragm (D), intercostal (I), scalenes (S), and sternomastoid (N). Lung volume ranges from end-expiratory position (EEP) to inspiratory capacity (IC). At the near right is the Mean and S.E. for muscle pressure and the four EMG measurements over the volume range. To the far right is the overall EMG Mean and S.E. for the four muscles combined (symbol x).

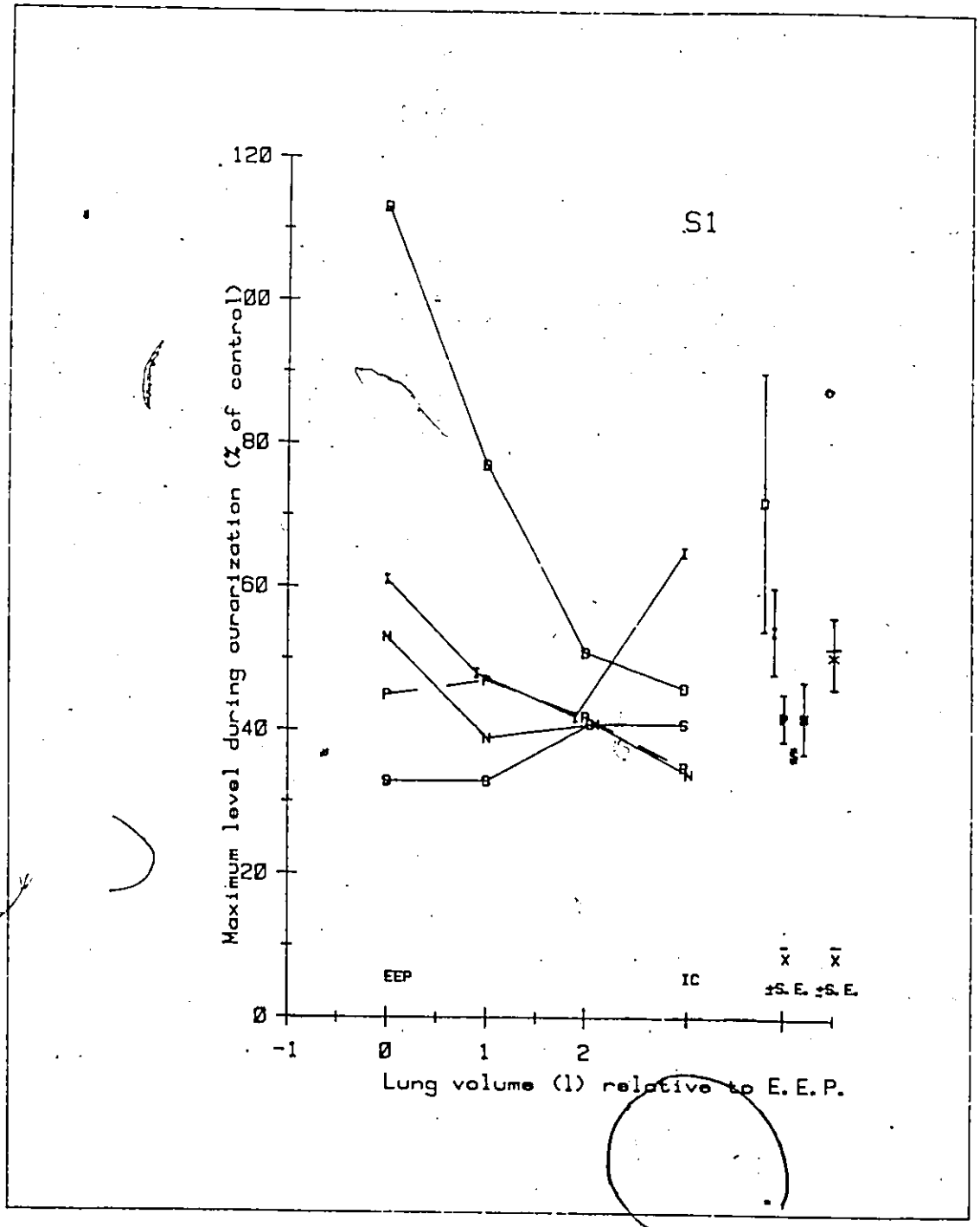

S1
120
100
80
60
40
20
0
Maximum level during curarization (% of control)
EEP
IC
±S.E.
±S.E.
-1
0
1
2
Lung volume (l) relative to E.E.P.

Figure 32. Maximum rectified EMG_{rms} and respiratory muscle pressure during curarization compared to control at four lung volumes in subject 2.

Legend same as Figure 31.

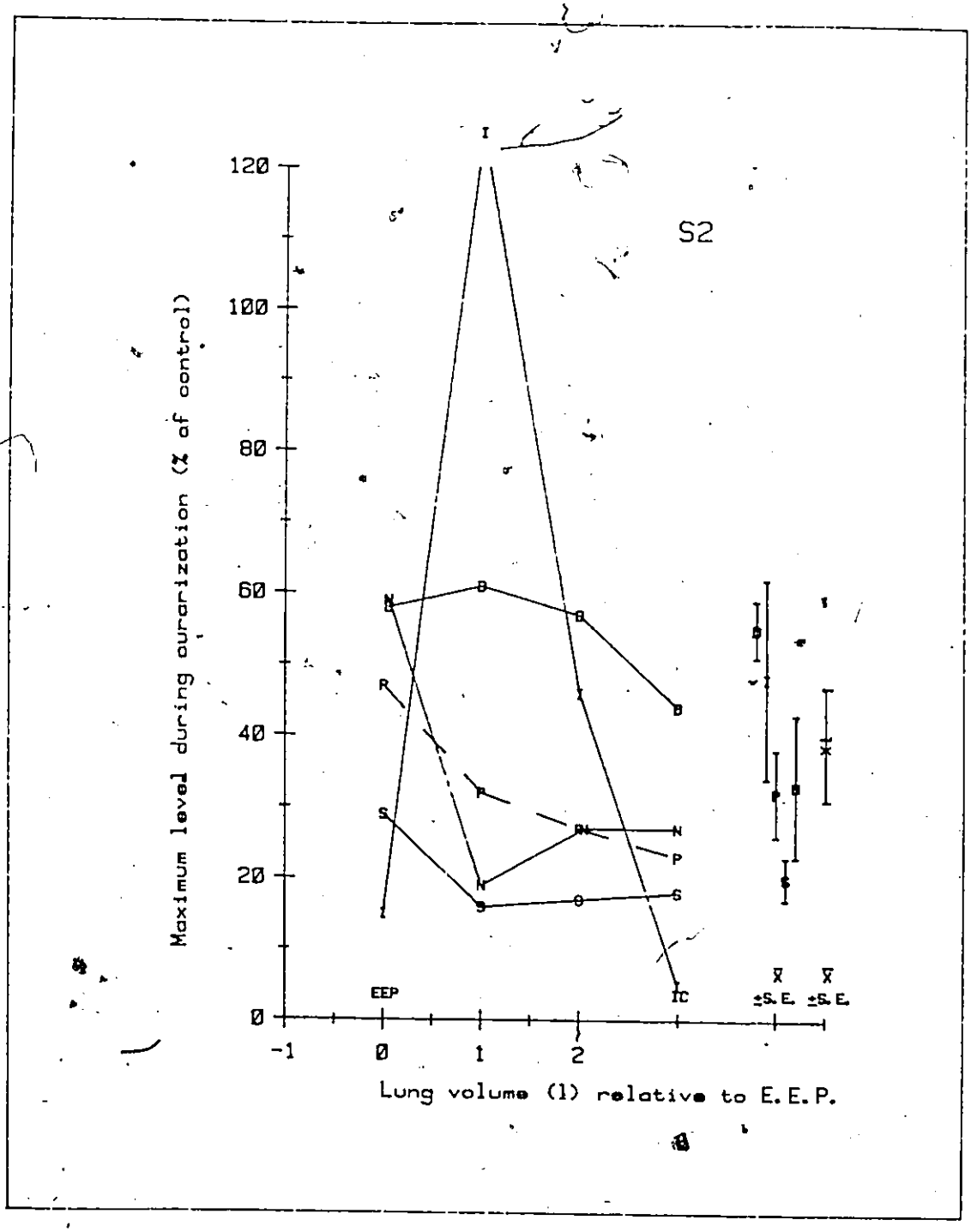

S2
Maximum level during aurarization (% of control)
120
100
80
60
40
20
0
-1
0
1
2
EEP
IC
X ±S.E.
X ±S.E.
Lung volume (l) relative to E.E.P.

Figure 33. Maximum rectified EMG and respiratory muscle pressure during curarization compared to control at four lung volumes in subject 3.

Legend same as Figure 31.

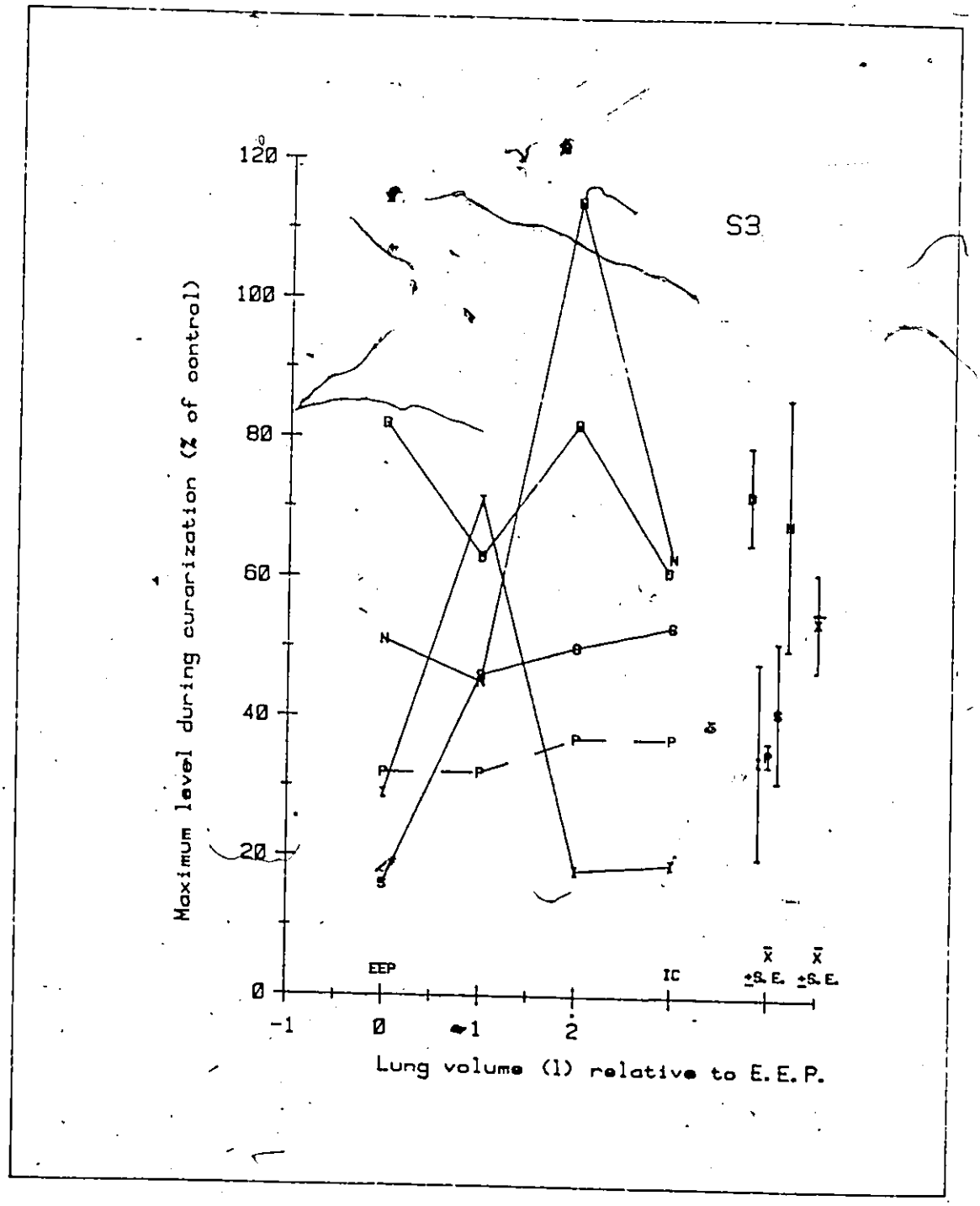

S3
Maximum level during curarization (% of control)
120
100
80
60
40
20
0
EEP
IC
X ±S.E.
X ±S.E.
-1
0
1
2
Lung volume (l) relative to E.E.P.

Figure 34. Maximum rectified EMG and respiratory muscle pressure during curarization compared to control at four lung volumes in subject 4.

Legend same as Figure 31.

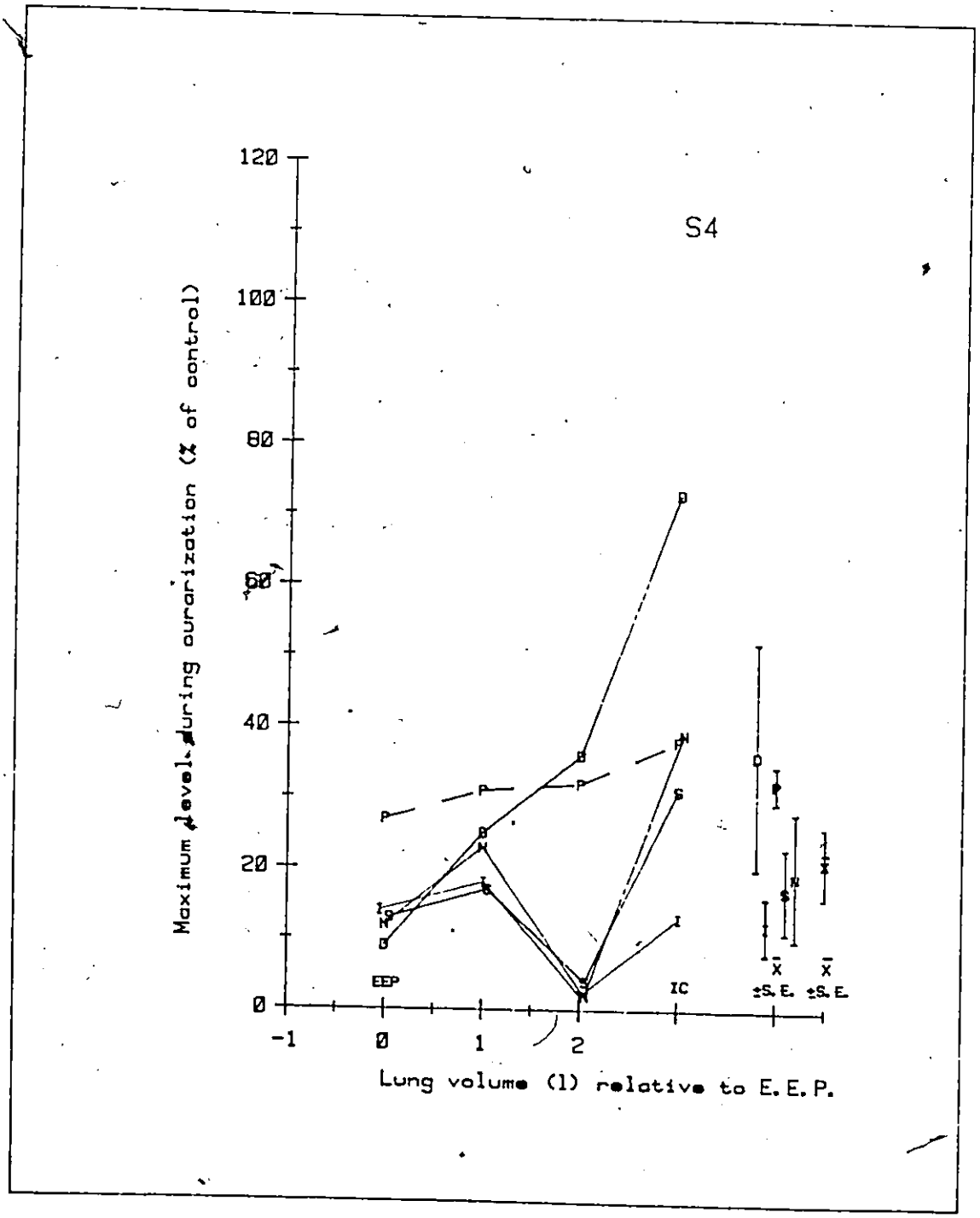

S4
120
100
80
60
40
20
0
Maximum level during curarization (% of control)
EEP
IC
±S.E.
±S.E.
-1
0
1
2
Lung volume (l) relative to E.E.P.

Figure 35. Maximum rectified EMG and respiratory muscle pressure during curarization compared to control at four lung volumes in subject 5.

Legend same as Figure 31.

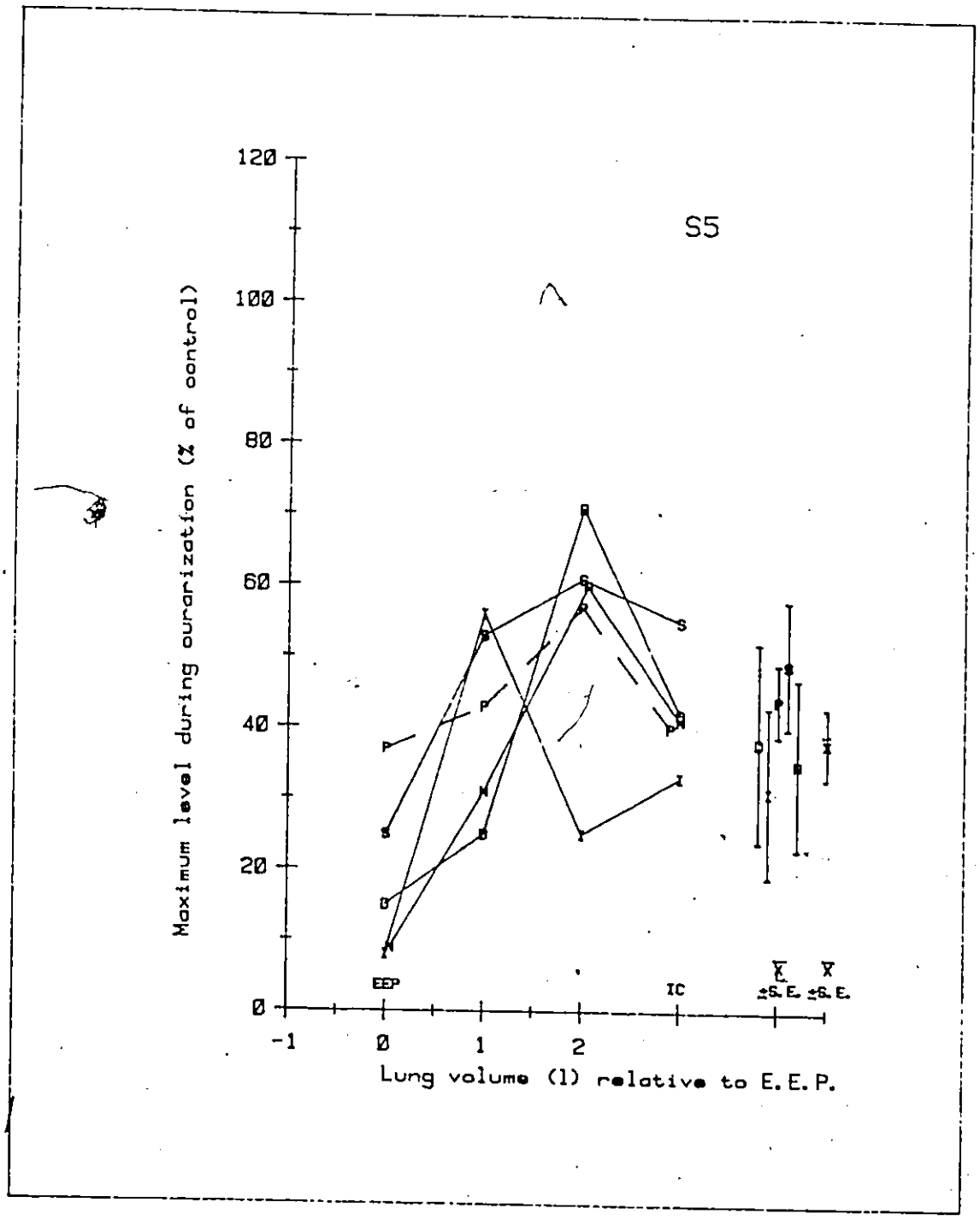
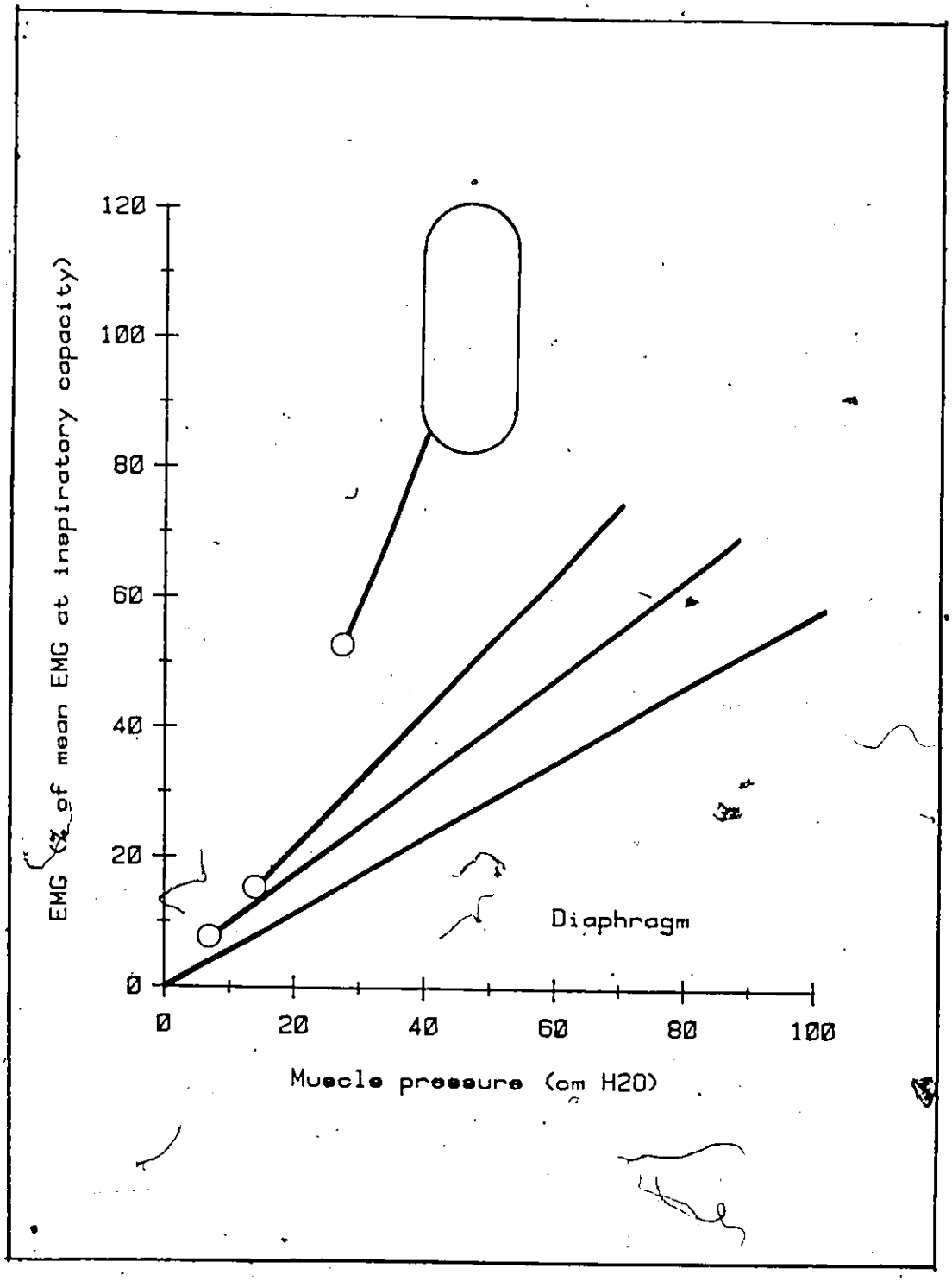
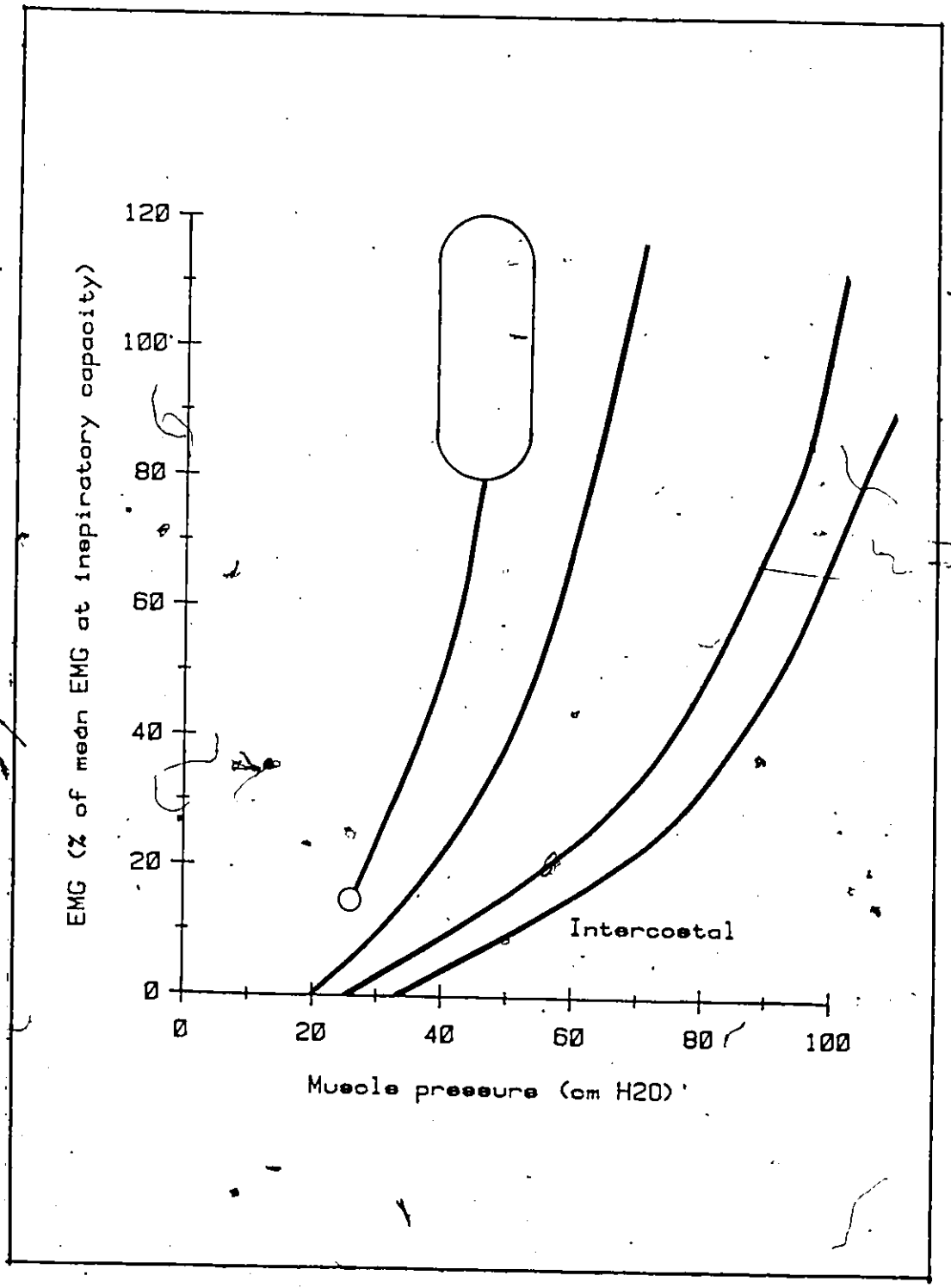
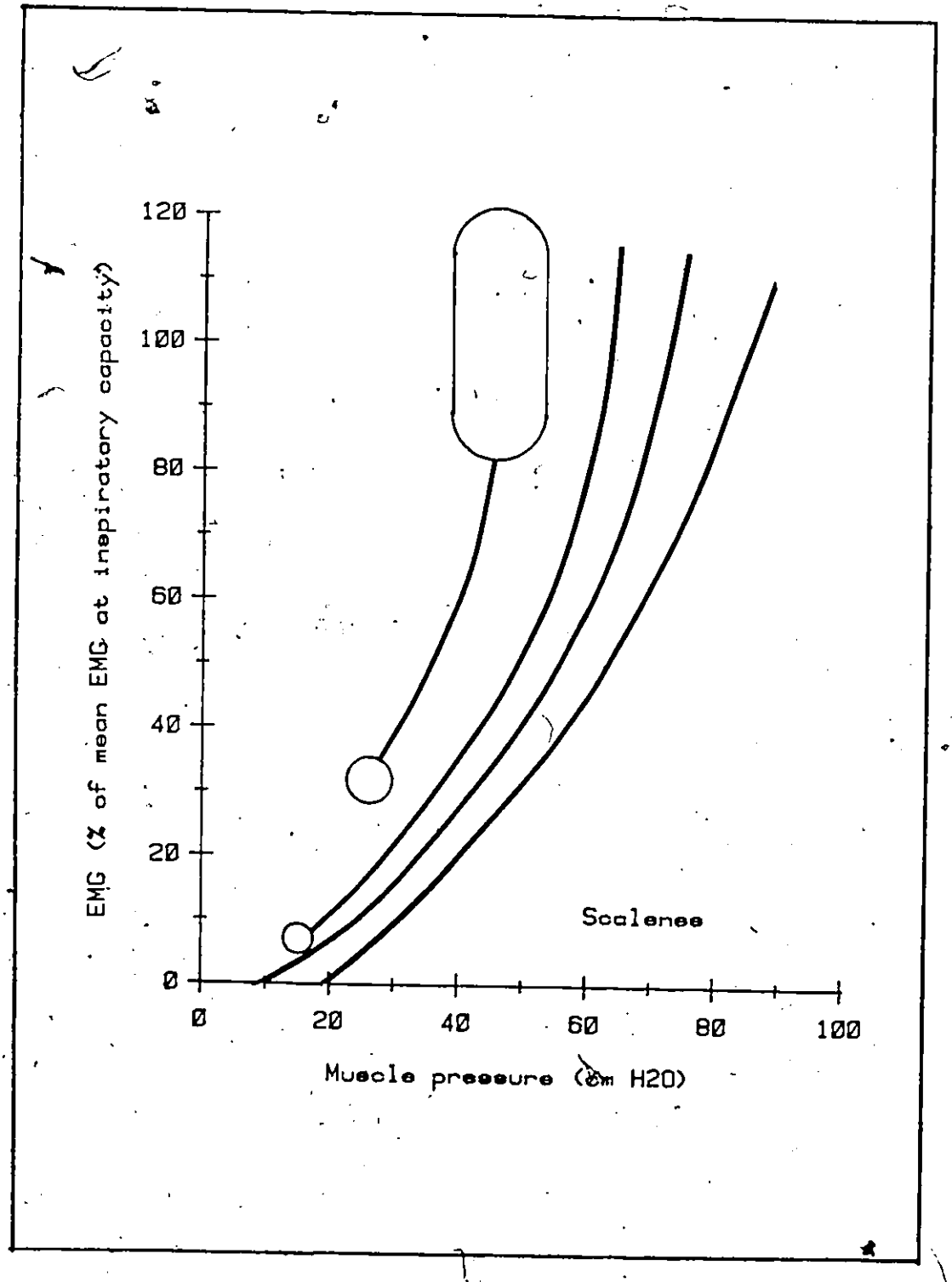

S5
120
100
80
60
40
20
0
Maximum level during ouarization (% of control)
-1
0
1
2
EEP
IC
X ±S.E.
X ±S.E.
Lung volume (l) relative to E.E.P.

Figure 36a-d. Schematic representation of rectified EMG of four inspiratory muscles for different muscle pressures over inspiratory capacity range.

The four curves starting from right to left represent efforts at the end-expiratory position, at 1 l above e.e.p., at 2 l above e.e.p., and at 3 l above e.e.p. The enclosure at the top of the figure approximates the range of EMG values while holding inspiratory capacity.


120
100
80
60
40
20
0
EMG (% of mean EMG at inspiratory capacity)
0
20
40
60
80
100
Muscle pressure (cm H2O)
Diaphragm


120
100
80
60
40
20
0
EMG (% of mean EMG at inspiratory capacity)
0
20
40
60
80
100
Muscle pressure (cm H2O)
Intercostal


EMG (% of mean EMG at inspiratory capacity)
120
100
80
60
40
20
0
0
20
40
60
80
100
Muscle pressure (cm H2O)
Scalenes

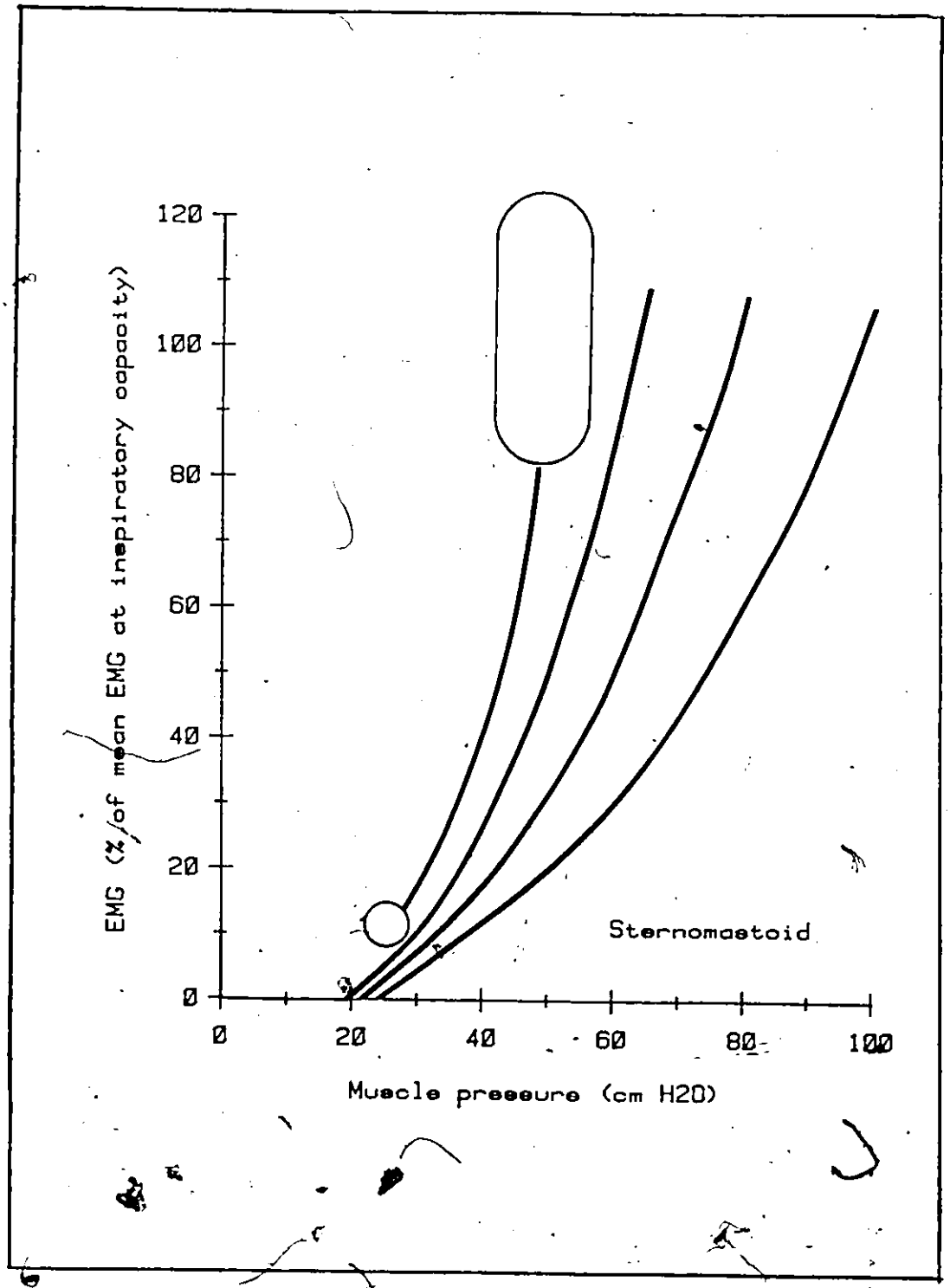
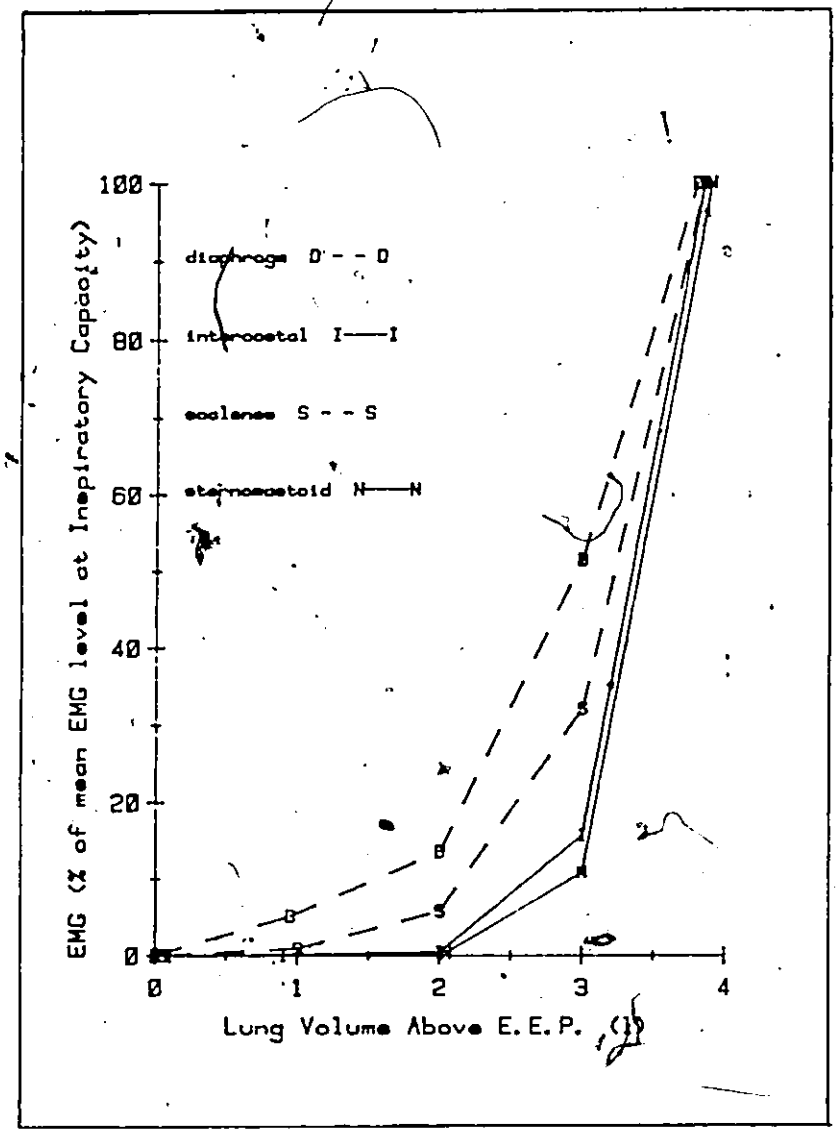

120
100
80
60
40
20
0
EMG (% of mean EMG at inspiratory capacity)
Sternomastoid
0
20
40
60
80
100
Muscle pressure (cm H2O)

Figure 37a. Mean level of rectified EMG for 5 subjects measured while maintaining different inspired lung volumes with open glottis (page 266).

The symbols are: diaphragm (D - - D), intercostal (I----I), scalenes (S - - S), and sternomastoid (N----N). Alveolar pressure is atmospheric.

Figure 37b. Mean level of rectified EMG for 5 subjects measured while producing inspiratory alveolar pressure at different lung volumes so that muscle pressure is equal to that at inspiratory capacity.

Symbols are for diaphragm (D - - D), intercostal (I----I), scalenes (S - - S), and sternomastoid (N----N).


100
80
60
40
20
0
diaphragm D - - D
intercostal I——I
scalenes S - - S
sternocostoid N——N
EMG (% of mean EMG level at Inspiratory Capacity)
0
1
2
3
4
Lung Volume Above E.E.P. (l)

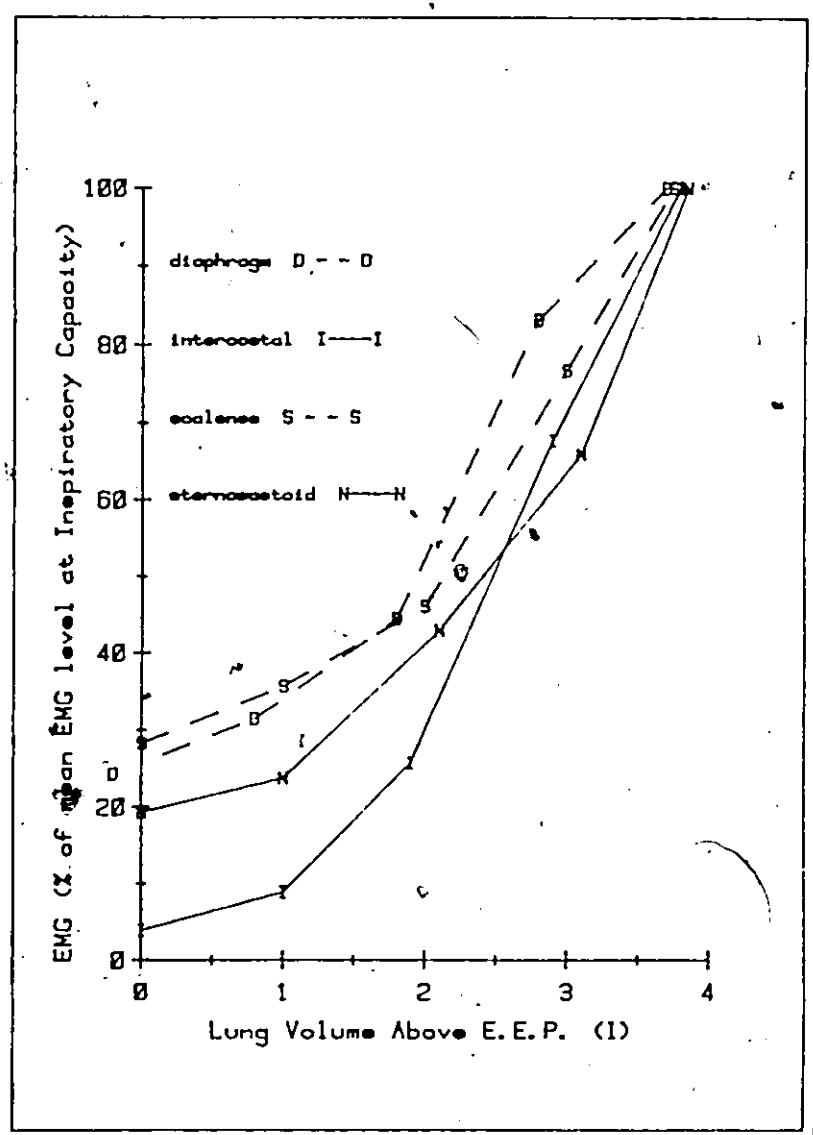

100
80
60
40
20
0
diaphragm D - - D
intercostal I——I
scalenes S - - S
sternocostoid N——N
EMG (% of mean EMG level at Inspiratory Capacity)
0
1
2
3
4
Lung Volume Above E.E.P. (l)

Figure 38. Level of force produced at varying firing frequencies in two muscles consisting of functionally different motor units.

Cycle time is interval between impulses at that frequency.

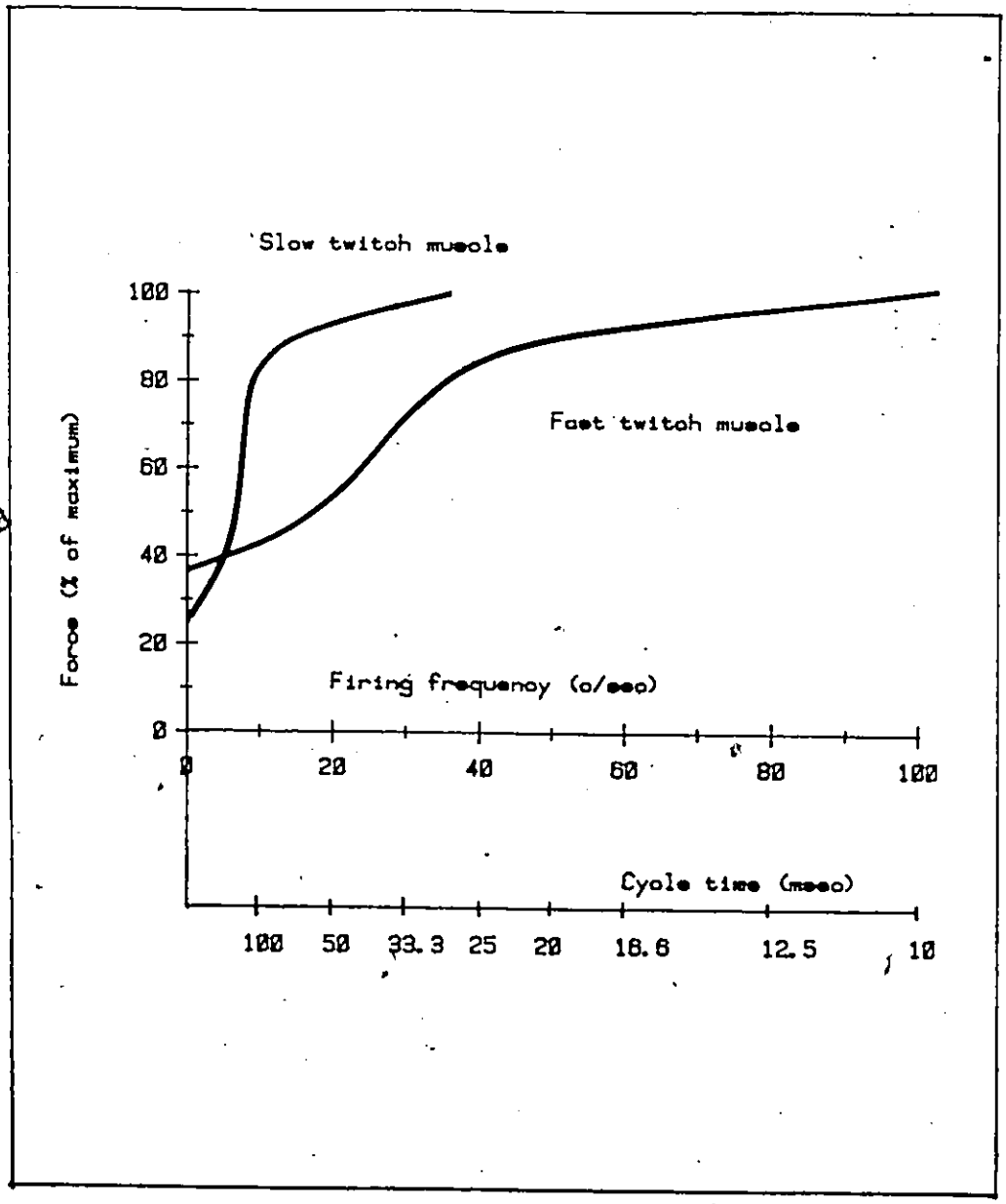

Slow twitch muscle
Fast twitch muscle
Force (% of maximum)
100
80
60
40
20
0
Firing frequency (o/sec)
0
20
40
60
80
100
Cycle time (msec)
100
50
33.3
25
20
16.6
12.5
10

Figure 39. Total time elapsed for completion of successive action potentials at different motor unit firing frequencies.

Example, if first impulse passed at time 0, the fourth impulse for a motor unit firing at 30 c/sec would occur 100 msec later. Lines a, b, c, d: hypothetical durations of block of acetylcholine receptors by curare.

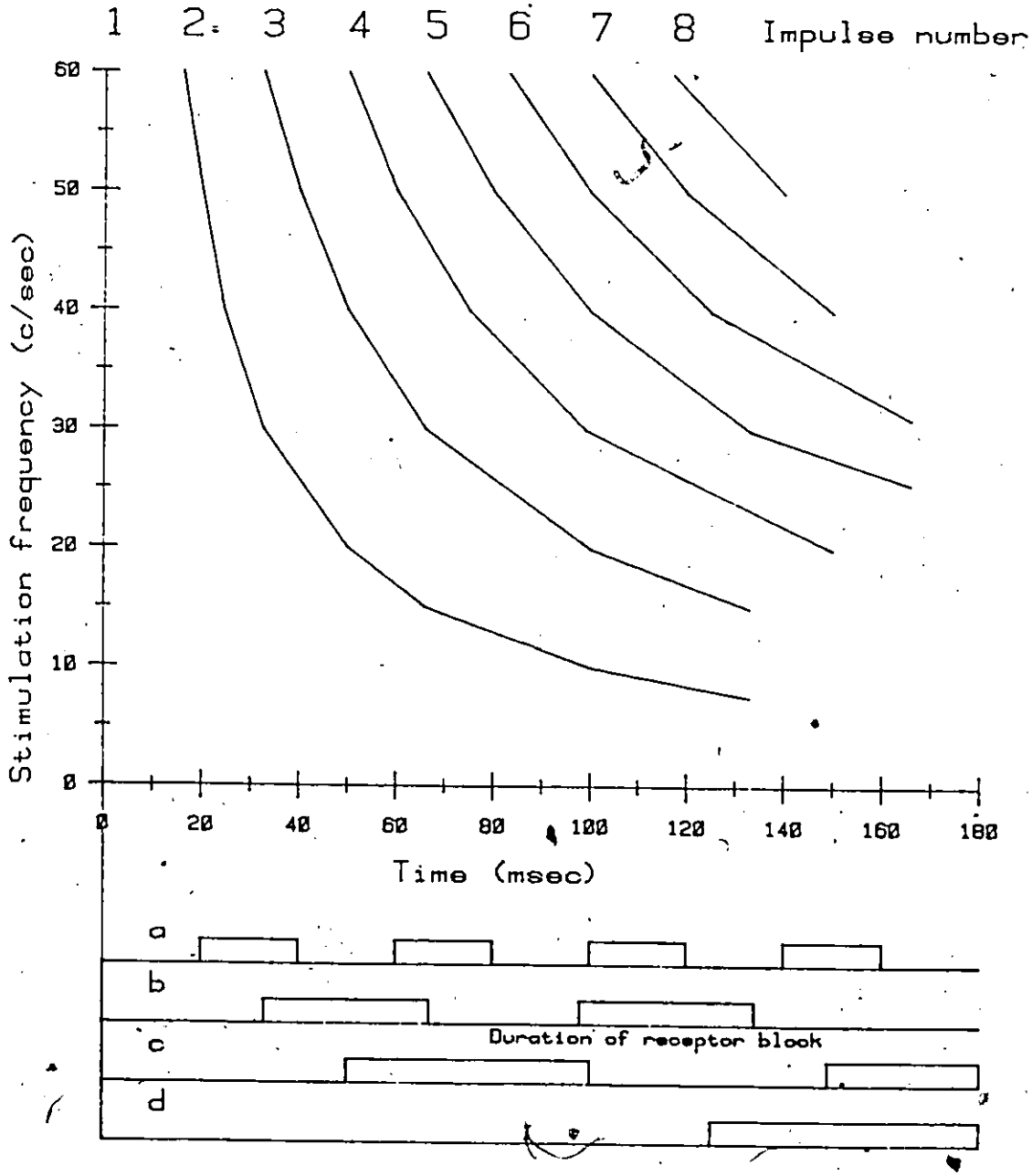

1 2 3 4 5 6 7 8 Impulse number
60
50
40
30
20
10
0
Stimulation frequency (c/sec)
0 20 40 60 80 100 120 140 160 180
Time (msec)
a
b
c
d
Duration of receptor block

Figure 40. Maximal inspiratory alveolar pressure and inspiratory capacity during curarization compared to control.

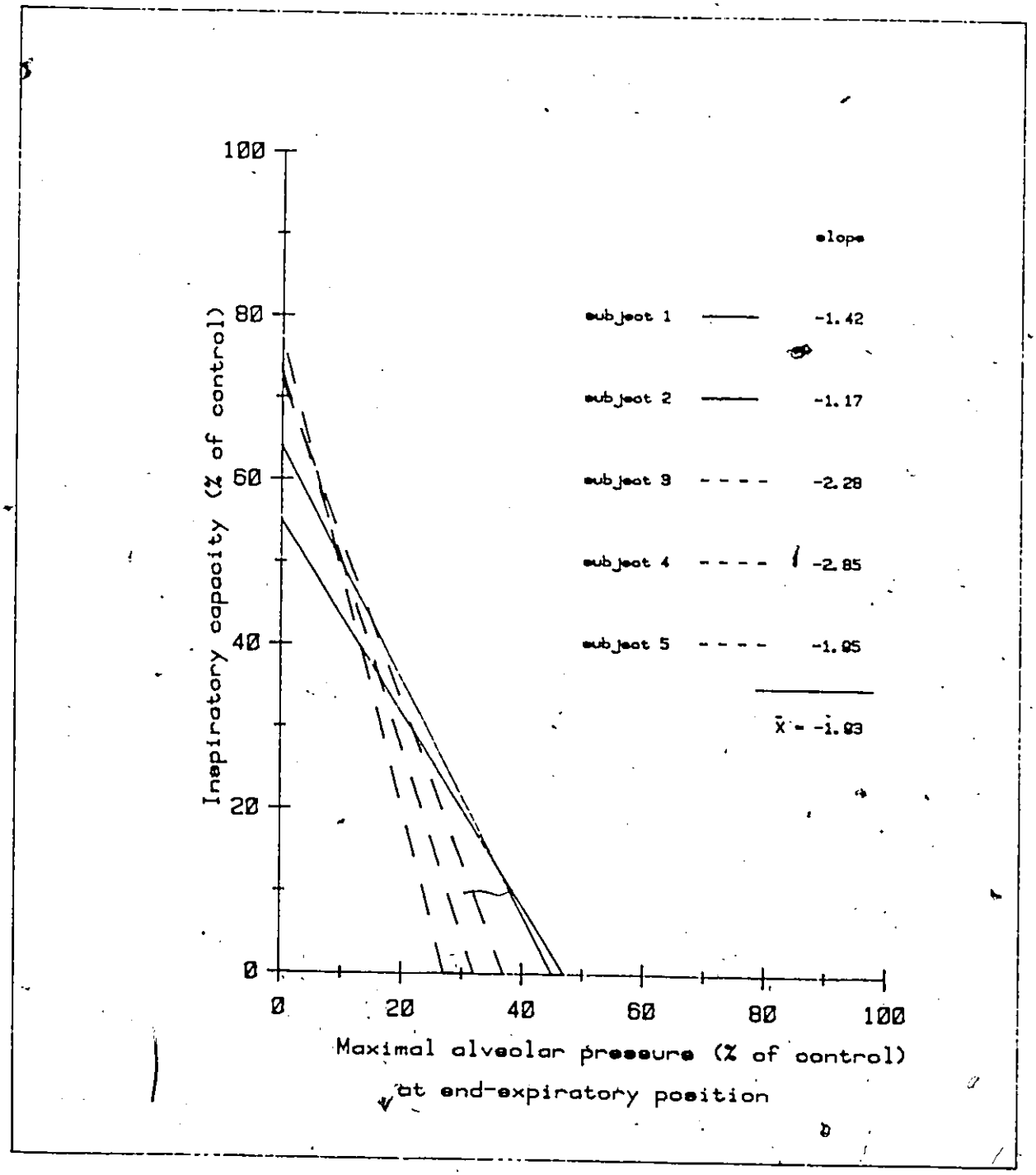

100
80
60
40
20
0
Inspiratory capacity (% of control)
0
20
40
60
80
100
Maximal alveolar pressure (% of control)
at end-expiratory position
slope
subject 1 -1.42
subject 2 -1.17
subject 3 -2.28
subject 4 -2.85
subject 5 -1.95
$\bar{x}$ = -1.93

Figure 41. Maximal inspiratory muscle pressure at end-expiratory position and at inspiratory capacity during curarization compared to control.

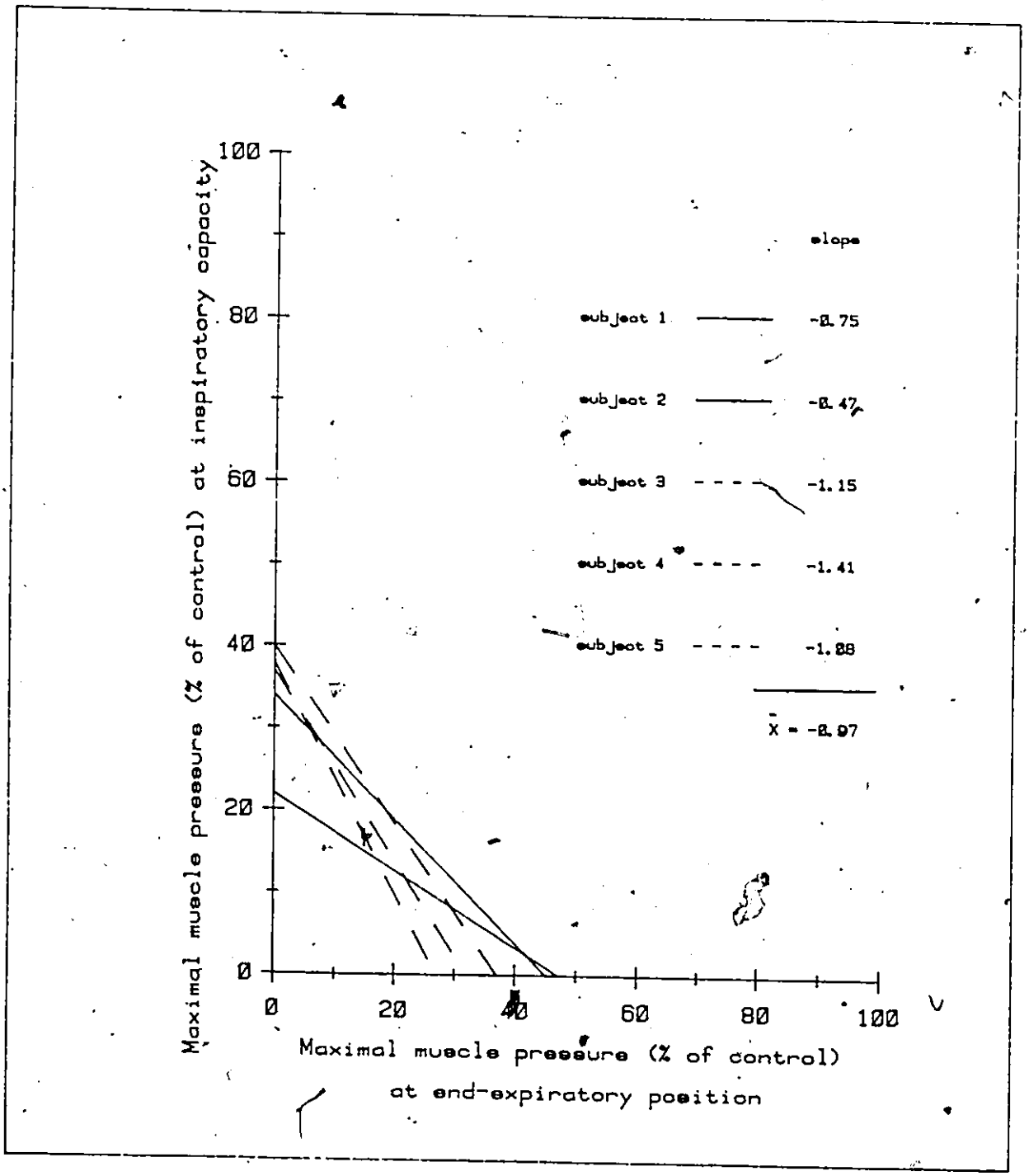

Maximal muscle pressure (% of control) at inspiratory capacity
100
80
60
40
20
0
0
20
40
60
80
100
V
Maximal muscle pressure (% of control)
at end-expiratory position
slope
subject 1 -0.75
subject 2 -0.47
subject 3 -1.15
subject 4 -1.41
subject 5 -1.88
X = -0.97

Figure 42. Location of end-expiratory lung position on Campbell pressure-volume diagram.

Normal position located at A. Point B would result from a more elastic lung (- -). A displaced chest wall characteristic (- -) would produce end-expiratory position at C. Location D would result if both lung and chest wall passive characteristics (-Pst(l), Pst(w)) were affected.

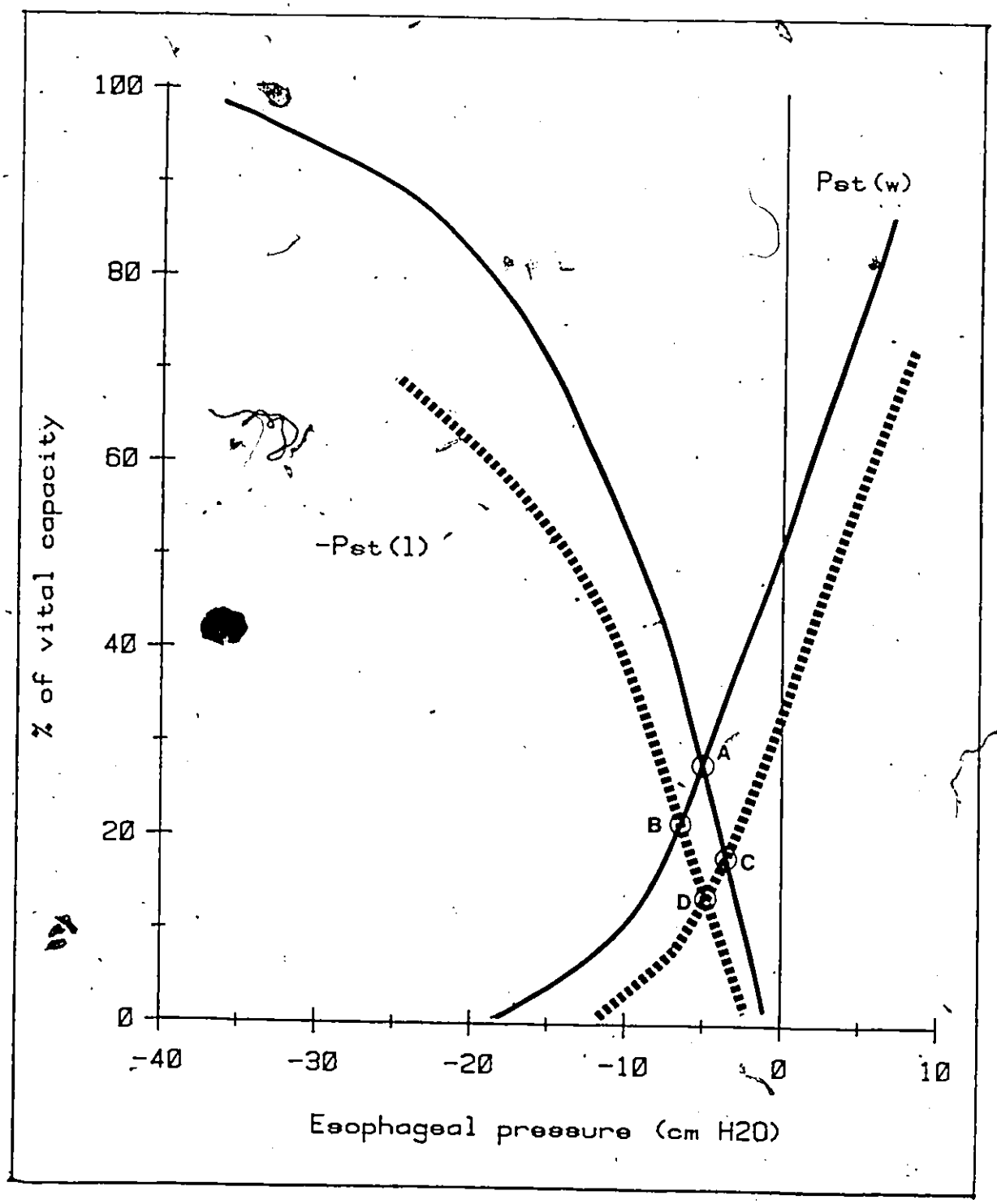

100
80
60
40
20
0
% of vital capacity
Pst(w)
-Pst(l)
A
B
C
D
-40
-30
-20
-10
0
10
Esophageal pressure (cm H2O)

Table 1: Characteristics of subjects.

Subject	Age (yrs)	Weight (kg)	Height (cm)	Vital Capacity (ml)	Vital Capacity (% of predicted)
1. SR	27	77.3	183	5110	94
2. JK	28	70.5	183	5130	95
3. LS	25	70.5	175	5270	103
4. MH	22	79.5	175	6280	121
5. MC	56	79.5	183	5000	103
6 FB	30	74.1	170	5120	107

Table 2: Inspiratory Muscle Strength.

	Maximal Inspiratory Alveolar Pressure at End-expiratory Position			Inspiratory Capacity		
	Control	Curare		Control	Curare	
	(cm H_2O)	(cm H_2O)	(% control)	(l)	(l)	(% control)
S_1	116	52	45	3.45	2.20	64
S_2	116	54	47	3.20	1.75	55
S_3	98	31	32	3.30	2.40	73
S_4	85	23	29	4.35	3.35	77
S_5	100	37	37	3.60	2.60	72
$\bar{x}$	103	39	38	3.58	2.46	68
$\pm$ S.D.	13	13	8	.46	.59	9

Table 3: Passive mechanical characteristics of respiratory system.

Expiratory compliance over mid-lung volume range (l/cm H_2O)

		S_1	S_2	S_3	S_4	S_5	$\bar{x} \pm$ S.D.		t	p
C_{rs}	control	0.12	0.15	0.11	0.13	0.12	.126	.015		
	curare	0.11	0.14	0.11	0.16	0.13	.13	.021	-0.534	N.S.
C_L	control	0.17	0.29	0.29	0.27	0.36	.276	.068		
	curare	0.15	0.23	0.23	0.26	0.35	.244	.072	2.764	0.05
C_W	control	0.42	0.28	0.21	0.23	0.18	.264	.094		
	curare	0.42	0.31	0.20	0.30	.22	.29	.087	-1.81	N.S.

Expiratory elastance (cm H_2O/l)

		S_1	S_2	S_3	S_4	S_5	$\bar{x} \pm$	S.D.	t	p
E_{rs}	control	8.3	6.7	9.1	7.7	8.3	8.0	0.89		
	curare	9.1	7.1	9.1	6.3	7.7	7.9	1.23	0.414	N.S.
E_L	control	5.9	3.4	3.4	3.7	2.8	3.8	1.19		
	curare	6.7	4.3	4.3	3.8	2.9	4.4	1.41	2.97	0.05
E_W	control	2.4	3.6	4.8	4.3	5.6	4.1	1.22		
	curare	2.4	3.2	5.0	3.3	4.5	3.7	1.05	1.77	N.S.

rs, L, and W represent respiratory system, lung and chest wall respectively.

Table 4: Esophageal pressure* at different lung volumes.

Lung Volume	Condition	S_1	S_2	S_3	S_4	S_5	$\bar{x} \pm S.D._x$		t	p
e.e.p	control	4.4	4.3	6.2	4.6	3.1	4.5	1.1		
	curare	2.3	5.9	4.4	2.0	2.0	3.3	1.8	1.6	<0.2
	p	<0.001	<0.001	<0.001	<0.001	<0.001				
e.e.p. + 1 l	control	11.7	9.3	11.8	9.2	9.7	10.3	1.3		
	curare	9.3	11.8	9.3	6.2	8.8	9.1	2.0	1.25	<0.5
	p	<0.001	<0.001	<0.001	<0.005	N.S.				
e.e.p. + 2 l	control	17.8	13.7	15.5	13.5	13.2	14.7	1.9		
	curare	16.3	14.3	13.6	9.8	10.5	12.9	2.7	2.56	<0.1
	q	N.S.	<0.02	<0.005	<0.001	<0.001				
inspiratory capacity	control	33.9	32.8	32.8	26.8	15.8	28.4	7.5		
	curare	19.5	15.6	18.0	17.2	11.8	16.4	2.94	5.1	<0.01
	p	<0.001	<0.001	<0.001	<0.001	<0.001				

* cm H_2O

Table 5: Esophageal pressure* change from end-expiratory position.

Lung Volume	Condition	S_1	S_2	S_3	S_4	S_5	$\bar{x} \pm$ S.D.		t	p
e.e.p	control	7.3	5.0	5.6	4.6	6.5	5.8	1.1		
+ 1 l	curare	7.0	5.9	4.9	4.3	6.8	5.8	1.2	0.07	$\leq$0.8
	p	N.S.	$\leq$0.02	N.S.	N.S.	N.S.				
e.e.p.	control	13.4	9.4	9.3	8.9	10.1	10.2	1.8		
+ 2 l	curare	14	8.4**	9.2	7.8	8.5	9.6	2.5	1.63	$\leq$0.2
	p	N.S.	$\leq$0.01	N.S.	N.S.	$\leq$0.005				
inspiratory	control	29.5	28.5	26.6	22.2	12.7	23.9	6,9		
capacity	curare	17.2	9.7***	13.6	15.3	9.8	13.1	3.3	3.95	$\leq$0.02
	p	$\leq$0.001	$\leq$0.001	$\leq$0.001	$\leq$0.001	$\leq$0.001				

* cm H_2O
** at 1.45 l
*** at 1.8 l

CHAPTER VIII

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