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Effect of hyperinflation on the diaphragm

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ABSTRACT: Acute hyperinflation causes the inspiratory muscles to operate at shorter than normal lengths. The ability of these muscles, in particular the diaphragm, to lower intrathoracic pressure is therefore reduced. Skeletal muscles, however, adapt to chronic shortening, and animals models of emphysema have shown that with chronic hyperinflation, the diaphragmatic muscle fibres lose sacromeres. As a result, the force-generating ability of these fibres is relatively preserved.

In patients with hyperinflation due to chronic obstructive pulmonary disease, the ability of the diaphragm to generate pressure is also better than anticipated on the basis of hyperinflation alone. However, the diaphragm in these patients is also lower in the chest wall than in healthy subjects. Consequently, even though the neural drive to the muscle is greater than normal, its ability to descend during inspiration is impaired. Its rib cage expanding action is also reduced; in patients with severe hyperinflation, contraction of the diaphragm even produces deflation, rather than expansion, of the rib cage. In such patients, therefore, the ability of the diaphragm to increase lung volume is reduced, and hence the act of breathing is more dependent on the rib cage inspiratory muscles.
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The airway and pulmonary abnormalities of chronic obstructive pulmonary disease (COPD) have several detrimental effects on the respiratory muscle pump. Firstly, the increased airflow resistance and reduced dynamic pulmonary compliance, characteristic of COPD, make the respiratory muscles work chronically against an increased load; this requires that the inspiratory muscles generate more force (or pressure) than normal to move air into the lung. Secondly, because of the inefficiency of the lungs as gas exchangers, minute ventilation is usually slightly greater in COPD than in normal subjects. Finally, COPD causes an increase in (static) functional residual capacity (FRC), so that the inspiratory muscles operate at shorter than normal lengths and have a reduced ability to lower intrathoracic pressure. In severe COPD, this alteration can be further accentuated by dynamic pulmonary hyperinflation [1, 2].

As pointed out by YOUNES [3], the increased load resulting from the increased airflow resistance and the decreased dynamic pulmonary compliance in COPD patients is small relative to the load that the respiratory muscles can compensate for and sustain. When normal subjects are given external resistances of the magnitude encountered in COPD patients, the alterations in maximum breathing capacity and maximal exercise tolerance are small [4]. On the other hand, the increase in end-expiratory lung volume imposes a severe stress on the inspiratory muscles, and there is substantial evidence indicating that the diaphragm, the primary muscle of inspiration in mammals, is more severely affected than the muscles of the rib cage. In this review, firstly, the effects of acute hyperinflation on the normal diaphragm will be analysed. Then, the response of the diaphragm to chronic, isolated hyperinflation, as observed in animal models of emphysema, will be examined. Finally, the abnormalities that have been observed in the diaphragm in patients with COPD will be summarized, and the effect of these abnormalities on the pattern of chest wall motion during breathing will be examined.

Effect of acute hyperinflation on the diaphragm

Pressure-generating ability

The influence of acute hyperinflation on the behaviour of the diaphragm as a pressure generator is primarily determined by the length-tension relationship. This relationship, which has been initially established *in vitro* by studies of single fibres from amphibian muscles [5], describes that property whereby the isometric tension developed by a skeletal muscle bundle during contraction (active tension) varies as a function of the resting length of the muscle before stimulation (fig. 1). Thus, as the relaxed length of the muscle increases, active tension increases until a maximum is reached. The resting length at which maximum active tension is reached is usually referred to as the optimal length (L_o); above this resting length, active tension gradually decreases. MCCULLEY and FAULKNER [6] have measured the length-tension properties of excised bundles of diaphragmatic

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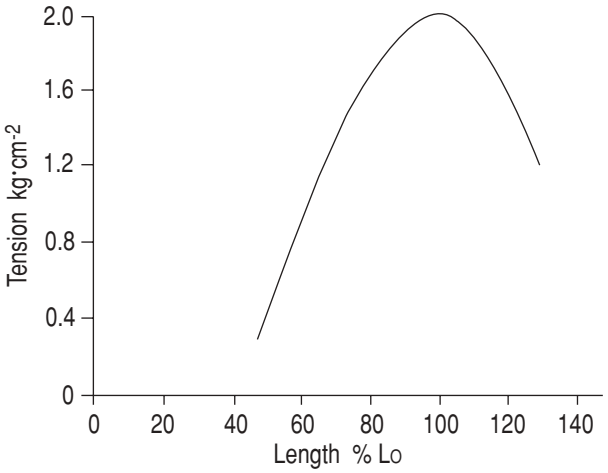

Fig. 1. – *In vitro* active length-tension relationship of a typical skeletal muscle. Length is expressed as percentage of the optimum force-generating length (*Lo*), and tension is expressed as kilograms per square centimetre of muscle cross-sectional area.

muscle fibres from five animal species (rats, cats, Rhesus monkeys, dogs and pigs), and have demonstrated that the diaphragm shows a similar relationship. Diaphragmatic muscle fibres *in vitro*, thus, produce progressively less force as their length is gradually decreased below their Lo; no active force can be generated when the muscle is shortened to approximately 50% of Lo.

The recent introduction of sonomicrometric techniques has allowed direct assessment of diaphragm length in animals. In supine anaesthetized dogs, increasing lung volume above FRC causes progressive shortening of the diaphragm; at total lung capacity (TLC) it is about 30% shorter than at FRC [7, 8]. Conversely, decreasing lung volume from FRC to residual volume (RV) lengthens the diaphragm by about 5%. Sonomicrometry has also established that, in supine dogs, the diaphragm at FRC is somewhat shorter than its *in vitro* optimal force-producing length (Lo) [8, 9]. In agreement with these findings, when the phrenic nerves in supine dogs and cats are selectively stimulated in the neck, the pressure generated by the diaphragm for a given stimulation decreases progressively as lung volume is increased above FRC [10–14]. Near TLC, the pressure generated by the contracting diaphragm is almost zero. MINH *et al*. [13] and SANT'AMBROGIO and SAIBENE [15] have even observed that, when the respiratory system in dogs and rabbits is passively inflated to a lung volume greater than 104% TLC, stimulation of the phrenic nerves induces a rise, rather than a fall, in airway pressure, indicating that the action of the diaphragm has become expiratory.

The response of the normal human diaphragm to hyperinflation is similar. Although there have been no direct measurements of diaphragmatic muscle fibre length in humans, BRAUN *et al*. [16] have combined posteroanterior and lateral chest radiographic images taken at different lung volumes, and autopsy measurements to demonstrate that the human diaphragm muscle shortens by 30–40% when lung volume is increased from RV to TLC. These figures are very close to those found in supine dogs. In addition, DANON *et al*. [17] have provided unequivocal evidence that the pressure-generating ability of the human diaphragm is closely dependent on lung volume. These investigators measured the fall in airway pressure and the pressure difference across the diaphragm (transdiaphragmatic pressure (P_{di})) in subjects with transection of the upper cervical cord, in whom bilateral pacing of the phrenic nerves in the neck allowed the diaphragmatic activation to be maintained at a constant level. When these subjects were supine at FRC and a valve was occluded at the mouth, the unassisted paced diaphragm was able to generate an adequate fall in airway pressure (40–60 cmH_2O) and an adequate P_{di}. However, the pressures produced by phrenic pacing decreased almost linearly as volume increased above FRC; at a volume of FRC +2.5 L, the fall in airway pressure was only 8–17 cmH_2O. A similar decline in the pressure-generating ability of the diaphragm with increasing lung volume has been found by SMITH and BELLEMARE [18] during bilateral stimulation of the phrenic nerves in normal subjects. As in animals, the human diaphragm virtually ceases to generate an inspiratory pressure at TLC.

It has long been thought that the dome of the diaphragm becomes flatter near TLC and that the increase in the radius of curvature contributed to the decrease in the pressure-generating ability of the muscle (Laplace's equation). However, KIM *et al*. [14] have observed, in supine dogs, that the relationship between active diaphragmatic tension (measured with a strain gauge) and P_{di} during phrenic nerve stimulation remained virtually unchanged as lung volume was increased from RV towards TLC; if an increase in the radius of curvature contributed to the decrease in P_{di} at high lung volumes, the ratio of active tension to P_{di} should have increased near TLC. Radiographic and nuclear magnetic measurements in normal humans have failed, in fact, to detect any significant change in shape of the diaphragmatic silhouette from RV to TLC [16, 19]. SMITH and BELLEMARE [18] have also pointed out that the relationship between lung volume and P_{di}, obtained during bilateral stimulation of the phrenic nerves in normal humans, is very similar to the length-tension relationship observed for diaphragmatic muscle bundles *in vitro*. It appears, therefore, that diaphragmatic shape plays little or no role in determining the effect of hyperinflation on the pressure-generating ability of the diaphragm in normal animals and humans.

Action on the rib cage

Acute increases in lung volume also affect the action of the diaphragm on the rib cage. When the normal diaphragm contracts alone at FRC, as in subjects with tetraplegia due to low cervical cord transection, there is a rise in abdominal pressure (P_{ab}) and an increase in abdominal dimensions, which is accompanied by a decrease (paradoxical motion) in the dimensions of the upper portion of the rib cage [17, 20–22]. This inspiratory contraction of the upper rib cage results from the fall in pleural pressure (P_{pl}) [23, 24]. At the same time, however, contraction of the diaphragm causes expansion of the lower rib cage. Indeed, the muscle fibres of the diaphragm originate from the upper margins of the lower six ribs and the xyphoid process of the sternum, and they run cranially, so that they are apposed directly to the inner aspect of the rib cage. Hence, when these fibres contract, they exert a force ("insertional" force) on the lower ribs, and, provided the abdominal visceral mass opposes the descent of the diaphragmatic dome effectively, this

force is oriented cranially, lifting the lower ribs and rotating them outward [25, 26]. In addition, the direct apposition of the normal diaphragm to the inner aspect of the rib cage makes the lower rib cage, in effect, part of the abdominal container [27]. In standing humans at rest, this "zone of apposition" of the diaphragm to the rib cage at FRC represents about 30% of the total surface area of the rib cage. Consequently, the rise in P_{ab} that takes place during inspiration is transmitted through the apposed diaphragm and pushes the lower rib cage outward [28]; this mechanism is usually referred to as the "appositional" component of diaphragmatic action.

As lung volume increases above FRC, the dome of the diaphragm descends relative to its costal insertions, decreasing the zone of apposition and increasing the area of the rib cage exposed to P_{pl}. Consequently, the diaphragm's expanding action on the lower rib cage decreases progressively [23, 25, 26, 29]. When lung volume approaches TLC, the zone of apposition becomes very small. Presumably, when phrenic nerve stimulation increases P_{pl} at large lung volumes, as described in animals [13, 14] and occasionally in normal humans [18], the zone of apposition is absent and the diaphragmatic muscle fibres at their insertions on the ribs are oriented transversally. With this geometry, the increase in P_{ab} no longer expands the lower rib cage, and the insertional force is expiratory rather than inspiratory in direction. Isolated contraction of the diaphragm then deflates the entire (lower and upper) rib cage.

The diaphragm in experimental emphysema

The hyperinflation of COPD, however, develops slowly over many years, and landmark experiments by TABARY, GOLDSPINK and co-workers [30–32] have shown that limb muscles can be extensively remodelled. Thus, when a limb muscle is immobilized for a few weeks in a lengthened position, sarcomeres are added; conversely, when a muscle is immobilized in a shortened position, sarcomeres are lost. Consequently, whereas acute reductions in muscle fibre length decrease the length of all the sarcomeres placed in series in the muscle fibres and produce a decrease in force (length-tension relationship), in chronically shortened muscles, the length of the individual sarcomeres is restored to virtually its initial length. The physiological result of this adaptation is that the active length-tension relationship is shifted toward shorter lengths but maximal tension remains normal (fig. 2).

To assess the effect of chronic hyperinflation on the diaphragm, SUPINSKI and KELSEN [33], FARKAS and ROUSSOS [34, 35], and KELSEN *et al*. [36] have used animal models of emphysema. A single intratracheal injection of papain or porcine pancreatic elastase in the rat or in the hamster produces, after a few weeks, similar anatomical lesions to those observed in severe panlobular emphysema in humans. Changes in lung volume (increases in FRC and TLC) and in the static pressure-volume curve (increase in static pulmonary compliance, reduction in lung recoil pressure) are also similar in direction to those seen in severe human emphysema.

With chronic hyperinflation in the hamster, there is a 10–15% loss of sarcomeres in the diaphragmatic muscle fibres. The active length-tension relationship of the muscle measured *in vitro* is, thus, shifted towards shorter

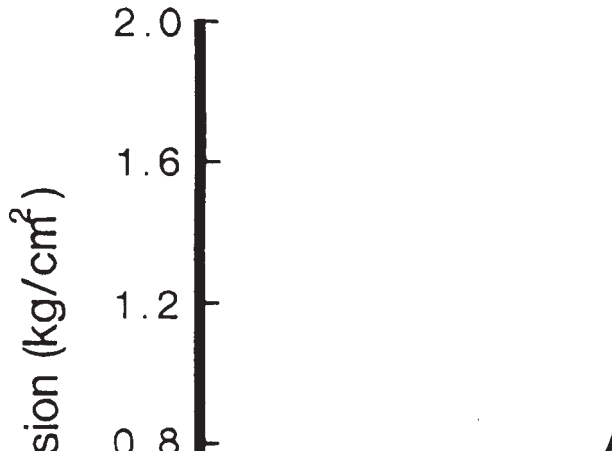

Fig. 2. – Diagram illustrating the effects of chronic shortening on the active length-tension relationship of a limb muscle. Note that, in contrast to figure 1, muscle length is expressed as absolute values (cm). With chronic shortening, the relationship is shifted to the left and the optimum force-generating length (*L*O) is reduced, but maximum tension (expressed as kg·cm^{-2}) remains normal.

lengths, and *in vivo* the pressure-generating ability of the muscle is relatively preserved. At any comparable (absolute) lung volume, the P_{di} developed during spontaneous inspiratory efforts against an occluded valve or during selective stimulation of the phrenic nerves is substantially greater in emphysematous than in control animals [37]. The diaphragm in emphysematous animals has, thus, a greater than normal ability to generate pressure at large lung volumes. Its pressure-generating ability, however, is not fully restored. Indeed, the maximal P_{di} that can be generated is lower than in control animals [37]; this is probably because the very large increase in lung volume induced by experimental emphysema increases the radius of curvature of the diaphragm.

The diaphragm in COPD

Although the experimental emphysema model in rodents has provided much useful information, it has some obvious deficiencies. In hamsters, long bones continue to grow in adult life, allowing structural adjustments in the rib cage, which are unlikely to occur in elderly humans. In addition, the rodent model of emphysema leads to unusually large increases in lung volume and is not associated with any increase in airway resistance and decrease in dynamic pulmonary compliance [37], so characteristic of COPD. This additional increase in inspiratory load in COPD could have a further training effect, improving respiratory muscle strength and endurance. Finally, the model does not reproduce the loss of body weight often found in advanced COPD.

Structural changes in the diaphragm

Studies of the structure of the diaphragm at autopsy in patients with COPD have produced inconsistent results. Thus, STEELE and HEARD [38] found that the diaphragm in 15 patients with COPD was reduced in thickness, volume and area, compared to that in 23 control subjects. BUTLER [39] similarly observed a reduction in the surface area of the diaphragm, particularly of the muscular portion, in 95 patients with COPD; there was a greater

reduction in diaphragm area when emphysema was more severe. The thickness of the diaphragm, however, was maintained. THURLBECK [40] also observed a reduction in diaphragm weight in patients with COPD and a negative correlation between the amount of emphysema and diaphragm weight. In contrast, ISHIKAWA and HAYES [41] observed that the diaphragm of nine patients with COPD had the same area and was thicker than in their 14 control subjects. Histologically, two of their patients with COPD also had thicker muscle fibres in the diaphragm compared to the control subjects. SCOTT and HOY [42] also observed that the average cross-sectional area of the diaphragmatic muscle fibres was increased in patients with COPD, whereas SANCHEZ *et al*. [43] reported this cross-sectional area to be smaller in COPD patients than in control subjects.

There are a number of factors which may account for these conflicting results. Firstly, postmortem changes (rigor mortis) may occur in the diaphragm, and excision may lead to variable muscle shortening. Secondly, COPD has sometimes been assessed by the severity of emphysema, which may not always be closely related to the degree of airflow obstruction and disability in life. Thirdly, many series consist of relatively few cases, and the effects of body weight and sex have sometimes been ignored, although studies have shown that the diaphragm weighs more in males than in females [40]. Furthermore, diaphragm weight and thickness are related to body weight; diaphragm weight and thickness are decreased in underweight patients with chronic nonrespiratory illnesses compared to patients dying suddenly or from acute illnesses, whereas both are increased in muscular labourers [44]. Loss of diaphragm weight and thickness in many COPD patients might, thus, be only part of the general skeletal muscle-wasting commonly observed in these patients. Comparing the diaphragm in 18 patients with COPD to that in 16 age-matched normal males, ARORA and ROCHESTER [45] found that, on average, the diaphragm in the patients was reduced in weight. When females and several underweight males were excluded from the comparison, however, the differences in diaphragm weight were considerably reduced.

Length of the diaphragm in vivo

In vivo diaphragmatic muscle fibre length in COPD patients has been estimated from chest radiographs. In studies of 21 males with moderately severe or severe COPD (results of pulmonary function tests were not provided) and 23 normal subjects, SHARP *et al*. [46] found that at FRC the diaphragms of the patients were about 40% shorter than normal; this value is close to the 30–40% shortening observed in healthy subjects on inspiration from RV to TLC [16]. ROCHESTER and BRAUN [47] have also made radiographic comparisons of diaphragm muscle length between 32 patients with COPD (forced expiratory volume in one second (FEV_1) 35% of predicted; TLC 112% pred; RV 70% of predicted TLC) and 22 healthy subjects. Computing an index of diaphragmatic muscle fibre length at FRC for both groups of subjects, they also found that, on average, the diaphragm muscle was 28% shorter in the patients than in the healthy subjects. As anticipated, diaphragm shortening was greater when hyperinflation was more severe, but the relationship between diaphragm length and lung volume (expressed as percentage of predicted TLC) in the patients was essentially similar to that observed in the healthy subjects.

Pressure-generating ability

SIMILOWSKI *et al*. [48] have recently measured P_{di} during bilateral stimulation of the phrenic nerves with single twitches in eight patients with COPD and hyperinflation (FRC = 140–180% pred; TLC = 116–136% pred). Twitch P_{di} at FRC ranged 10.9–26.6 cmH_2O, and while these values were lower than those found at FRC in five age-matched healthy subjects (26.2±3.6 cmH_2O), they were higher than expected on the basis of the increased lung volume. However, these patients had a low, flat diaphragm, which might have caused further reduction in P_{di}. This would suggest that patients with COPD and hyperinflation lose sarcomeres in series in the same way as emphysematous hamsters do, although the chronic overload imposed by the disease on the diaphragm (leading to chronic hypertrophy) may also play a role. In addition, whereas positive pleural (oesophageal) pressures were generated by twitches at TLC in one of the normal control subjects, no positive pleural pressures were seen in the patients, despite an average TLC which was 124% pred. Indeed, at any given absolute lung volume, the patients converted a greater fraction of the twitch P_{di} into a negative P_{pl} than the control subjects [48], indicating relative preservation of the inspiratory capacity of the diaphragm.

Volume displacement during breathing

Although the pressure-generating ability of the diaphragm in patients with COPD is better than anticipated on the basis of hyperinflation alone, the muscle cannot increase lung volume like a normal diaphragm. Indeed, the primary mechanism of the diaphragmatic contribution to tidal volume in normal humans is a piston-like axial displacement of the dome related to the shortening of the apposed muscle fibres, and in patients with COPD and hyperinflation, the diaphragm is flatter and lower than in normal subjects. The zone of apposition is, therefore, reduced in size, so that when the muscle contracts the ability of the dome to descend is less than in normal subjects. As a result, the rise in abdominal pressure and the expansion of the ventral wall of the abdomen are smaller. Because of the reduced zone of apposition and the smaller rise in abdominal pressure, the expansion of the lower rib cage due to diaphragmatic contraction is also smaller than in normal subjects (decreased appositional force). In some patients with severe hyperinflation, the normal curvature of the diaphragm is even reversed at TLC, with its concavity facing upward, rather than downward. The zone of apposition has then completely disappeared, and the muscle fibres at their insertions on the ribs run transversally inward, rather than cranially. In this condition, the contraction of the diaphragm no longer expands the abdomen, and produces an inspiratory decrease in the transverse diameter of the lower rib cage [49, 50].

LEVINE *et al*. [51] have measured the swings in abdominal and pleural pressure during resting breathing in 11 patients with moderately severe COPD (FEV_1 = 1.0 L)

and eight control subjects; they found that for a given fall in P_{pl}, the rise in P_{ab} was smaller in the patients. MARTINEZ *et al*. [52] have made similar measurements in 45 patients with varying degrees of airflow obstruction and hyperinflation; they also observed that as airflow obstruction and hyperinflation became more severe, the rise in P_{ab} decreased relative to the fall in P_{pl} (fig. 3). In patients with severe disease, the inspiratory fall in P_{pl} was even associated with a decrease in P_{ab} and a reduction in abdominal dimensions, thus confirming that, in such patients, the rib cage inspiratory muscles (scalenes, inspiratory intercostals) make a greater contribution to tidal volume than the diaphragm.

The fact that patients with severe COPD may have rib cage expansion with an inward abdominal motion during resting inspiration had been recognized in earlier measurements of thoracoabdominal motion [46, 53, 54], and this had led to the widespread belief that these patients have less use of the diaphragm than healthy subjects, possibly due to diaphragmatic fatigue [52, 55]. Using needle electrodes inserted in the costal part of the right hemidiaphragm, however, we have recently measured the firing frequencies of large numbers of single diaphragmatic motor units during resting breathing in eight patients with severe COPD (FEV_1 = 0.82 L) and six control subjects of similar age [56]. All the motor units recorded in the control subjects and the patients discharged rhythmically in phase with inspiration. However, whereas the discharge frequency of all units in the control subjects averaged (mean±SD) 10.5±2.4 Hz, in the patients, the mean discharge frequency was 17.9±4.3 Hz. This is unequivocal evidence that, in patients with COPD, the neural drive to the diaphragm is markedly increased, rather than decreased. The reduced outward displacement of the ventral abdominal wall during inspiration must, therefore, result from mechanical factors

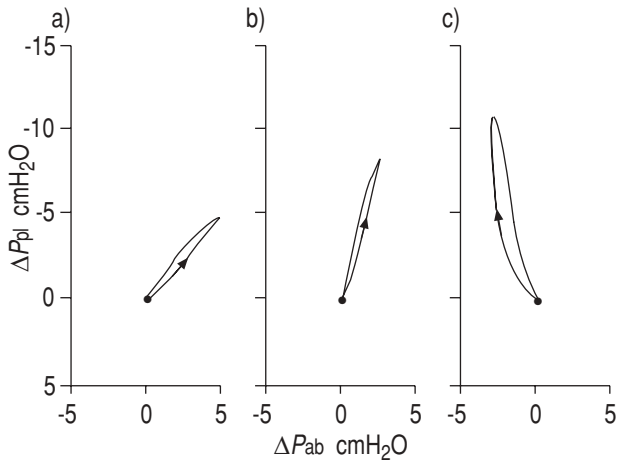

Fig. 3. – Inspiratory pressure generation during tidal breathing: a) in a normal subject; b) in a patient with moderately severe chronic obstructive pulmonary disease (COPD); and c) in a patient with severe COPD. The pleural pressure swing (ΔP_{pl}) is on the ordinate, and the abdominal pressure swing (ΔP_{ab}) is on the abscissa. The closed circle in each panel corresponds to end-expiration, and the arrow marks the inspiratory phase of the breathing cycle. In the normal subject, P_{ab} increases during inspiration by about as much as P_{pl} decreases. However, in the patient with moderately severe COPD, ΔP_{pl} is greater but ΔP_{ab} is smaller. The patient with severe COPD may have a decrease in P_{ab} during inspiration, which corresponds to a cranial displacement of the diaphragm and an inward displacement of the ventral abdominal wall. (Adapted from MARTINEZ *et al*. [52]).

alone (impaired ability of the low diaphragm to descend, vigorous contraction of the rib cage inspiratory muscles, and larger than normal decrease in P_{pl} to overcome the increased resistive and elastic loads).

Summary

In this paper, some physiological concepts that relate to the diaphragm in patients with chronic obstructive pulmonary disease have been reviewed. As these patients develop hyperinflation, their diaphragm becomes flatter and shorter. Chronic shortening possibly causes the diaphragmatic muscle fibres to lose sarcomeres, such that the force-generating ability of these fibres is relatively preserved. However, the low (caudal) position of the diaphragm in the chest wall makes it less effective in its inspiratory action, and, therefore, as the disease progresses, the act of breathing becomes gradually more dependent on the rib cage inspiratory muscles. The response of these muscles to hyperinflation will be examined in an accompanying communication.

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