The Respiratory Muscles in Chronic Obstructive Pulmonary Disease

Respiratory muscle function and activation in chronic obstructive pulmonary disease

David K. McKenzie,1,2 Jane E. Butler,2 and Simon C. Gandevia2
1Department of Respiratory and Sleep Medicine, and 2Prince of Wales Medical Research Institute, Prince of Wales Hospital and University of New South Wales, Randwick, Australia

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THE RESPIRATORY MUSCLES ARE unique among skeletal muscles, since they must work without sustained rest throughout life. The diaphragm is the principal inspiratory pump muscle, especially during sleep, and it is more resistant to developing fatigue than limb muscles in vivo and in vitro (e.g., Ref. 41). The inspiratory muscles recover from fatigue 10 times faster than the elbow flexors performing a similar task (70). The upper limit of blood flow to the diaphragm (adjusted for muscle mass) is two to four times that of most limb muscles, and there is a corresponding increase in the capillary density (69, 85). The volume density of mitochondria, the oxidative capacity of the muscle fibers, and maximal oxygen consumption of the diaphragm exceed those of limb muscles by two to six times (69, 85). The relatively small muscle fiber size of respiratory muscles also reduces the diffusion distance for oxygen (74). The diaphragm retains perfusion during relatively strong contractions, which would normally cause a rise in intramuscular pressure to levels greater than systolic arterial pressure, because the thin sheet of muscle produces a negative intrapleural pressure and provides a pressure gradient across the muscle to facilitate blood flow (12, 71).

As detailed in the first two mini reviews of this series (27, 65), the function of the respiratory muscles is compromised in patients with chronic obstructive pulmonary disease (COPD) for several reasons. These include increased resistive and elastic loads, large inequalities in time constants between different areas of lung, which means that effective compliance may be reduced, hyperinflation, which reduces the ability of the chest wall to inflate the lung and the less favorable length-tension relation of the respiratory muscles. Dynamic
hyperinflation and intrinsic positive end-expiratory pressure provide an additional inspiratory threshold load, and ventilation-perfusion mismatching in COPD means that ventilation must increase to maintain normocarbia.

As a result, drive to the inspiratory muscles must increase in patients with COPD. This is obvious in patients who defend their blood gases in the face of increased loads and ventilatory requirements. The “pink puffer” bracing his arms while struggling with inspiration and exhaling through pursed lips is a familiar sight, but what about the “blue bloaters” with hypercarbia and cor pulmonale? What is their inspiratory drive, and how can it be measured?

Evidence supporting the notion of increased inspiratory drive in COPD is reviewed below along with discussion of the limitations of different methods of measurement. The distribution of drive to the major inspiratory muscles is examined and compared with normal subjects. The altered mechanics and functional capacity of the diaphragm and rib cage in COPD are discussed. The implications for exercise and the response to lung volume reduction surgery are considered along with the role of sleep in the development of respiratory failure.

INCREASED INSPIRATORY DRIVE IN COPD

Methods used to measure respiratory drive have some limitations, especially in patients with COPD. Here, the abnormalities of gas exchange, increased loads, and impaired chest wall mechanics mean that measurements of ventilation and arterial CO₂ tension are poor indicators of drive.

During wakefulness, inspiratory drive includes a proportion of corticospinal (voluntary) inputs (42, 66, 88) in addition to those from the bulbopontine respiratory-related neurons. The latter are probably incapable of fully activating the diaphragm even when the chemical drive to breathe is high (93). By contrast, the diaphragm can be almost fully activated during maximal voluntary efforts in both healthy subjects (e.g., Refs. 8, 39) and patients with COPD (75, 94, 102). Voluntary drive may be required during severe exacerbations of airway disease (6), and its loss may contribute to the central hypoventilation in sleep in some patients with severe COPD (see below). Topel and colleagues (102) showed that maximal voluntary activation of the diaphragm was slightly greater in COPD patients with hypercapnia compared with normocapnic patients.

Respiratory drive during eucapnic tidal breathing has been assessed by a variety of methods. As drive increases, inspiratory flow increases due to increased velocity of shortening of inspiratory muscles. In COPD, transpulmonary pressure swings for a given tidal volume, and the rates of change of inspiratory flow and pressure increase (61). However, in COPD, flow and pressure changes are influenced by airway narrowing and altered lung mechanics as well as changes in drive. To overcome this problem, the mouth pressure 100 ms after occlusion of the mouthpiece (P₀.₁) was proposed as an index that would not be influenced by airway narrowing or altered respiratory compliance (105). This is increased three- to fivefold in severe COPD (7, 99), consistent with increased inspiratory drive. However, the method has several limitations. It is influenced by muscle strength, initial lung volume, muscle shortening during the occlusion, distortions of the chest wall, and tonic vagal input (104). It may also be affected by intrinsic PEEP. Furthermore, transient occlusion of inspiratory flow elicits a short-latency proprioceptive reflex in inspiratory muscles with inhibition occurring within ~40 ms (15, 21, 83), and the duration of the reflex inhibition is prolonged by airway disease (14). Despite these problems, P₀.₁ remains a useful noninvasive measure of drive as long as its limitations are understood (104).

Previous methods to evaluate the contribution of different inspiratory muscles to tidal ventilation in patients with COPD have included analysis of the separate pressure changes and/or motion of the thoracic and abdominal compartments (e.g., Refs. 68, 91, 92). The best index of inspiratory drive to individual respiratory muscles would be a measure of motoneurone pool output. A reasonable surrogate for this is the electromyographic (EMG) activity, usually measured by surface electrodes and normalized to the greatest activity recorded (e.g., Refs. 31, 45, 96). For the diaphragm, surface electrodes may be attached to an esophageal catheter to record crural EMG (80) or applied to the chest wall over the zone of apposition of the diaphragm. Chest wall electrodes have serious limitations: 1) they will record from other muscles including intercostal and abdominal muscles; 2) the signal-to-noise ratio is poor, particularly in obese subjects, and in hyperinflation the zone of apposition is short; 3) recordings are subject to large artifacts related to lung volume, diaphragm length, and posture (40).

Druz and Sharp (31) found, using esophageal electrodes, that diaphragmatic EMG appeared increased in patients with severe COPD compared with healthy individuals, a finding confirmed by others (45). However, early esophageal recordings of diaphragmatic EMG were also subject to large artifact changes in EMG amplitude with changes in lung volume and thoracoabdominal configuration (40). This problem is reduced using an esophageal catheter with multiple pairs of electrodes so that an optimal pair for recording can be selected as the crural fibers or catheter move (97). Using this device, Sinderby and colleagues (95) estimated that neural drive to the diaphragm was increased approximately fivefold in five patients with COPD compared with five control subjects. They expressed diaphragm EMG during resting ventilation as a percentage of that during a maximal inspiratory effort. This technique assumes that the subjects in both groups similarly recruit diaphragm, intercostal, and scalene muscles and activate the diaphragm to a similar degree in maximal efforts. Jolley and colleagues (54) used similar techniques in a much larger group of subjects. Age-matched healthy subjects (n = 26) required only 11% of “maximal” diaphragm activity during resting breathing compared with 28% in COPD patients (n = 30). In other words, respiratory drive was increased approximately threefold in the patients with COPD, and this measure of drive correlated inversely with measures of airway function.

Measurement of the discharge frequency of single motor units overcomes the problems of artifactual recording conditions, normalizing activity to “maximal” maneuvers, and assumptions about muscle length. Costal diaphragm activity is recorded via a needle electrode inserted through the seventh or eighth intercostal space close to the costal margin and below the pleural reflection (25). The mean discharge frequency of the motor units in severe COPD patients was 17.9 Hz, ~70% higher than that in age-matched control subjects (10.5 Hz; Fig. 1). By contrast, the relative increase in drive was only ~33% for the parasternal intercostal muscles (13.4 vs. 10.1
Data are shown for diaphragm (middle), scalene (space (1.2 liter) that increased ventilation threefold (Ve tidal, shaded bars) and during a period of stable breathing through a dead space (1.2 liter) that increased ventilation threefold (Ve tidal, shaded bars) and during a period of stable breathing through a dead space (1.2 liter)). The increased inspiratory drive in COPD results in higher firing frequencies of motor units in all three inspiratory muscles, with the largest increase in rate in the diaphragm. The increases in firing rates for the three muscles are similar to those observed in young healthy control subjects when ventilation is increased by threefold. Data are derived from three different studies using the same methodology for recording single motor units (25, 36, 38).

The single motor unit technique of measuring drive has limitations. First, as drive increases, it becomes difficult to discriminate and measure the discharge frequency of units. Second, as the method does not record all the active units in the muscle, it cannot measure accurately the recruitment of new units. It is possible that the diaphragm and other inspiratory muscles differed in their response to increased drive in terms of frequency modulation as opposed to recruitment. Finally, the functional significance of an increase in mean discharge frequency, in terms of mechanical output or chemical drive, is not intuitively obvious. To address the latter issue, the discharge of single motor units was recorded from three major inspiratory muscles in healthy subjects at rest and when ventilation was increased threefold by an external dead space (36). The mean discharge frequency of costal diaphragm single motor units increased approximately linearly by ~70% from 11.0 to 17.7 Hz, whereas that of the parasternals increased ~20% and the scalenes ~10% (Fig. 1). This suggests that the pattern of increased inspiratory activity in COPD patients, who had a disproportionate 70% increase in discharge frequency of the diaphragm motor units, may be similar to that in healthy subjects. The results also suggest that the total increase in inspiratory drive (due to both increased discharge frequency and recruitment) in the severe COPD patients was approximately threefold, as reported by Jolley (54) using esophageal recordings of crural EMG (Fig. 2). Combining the results for the increase in firing frequency and the increase in overall EMG activity, the increase in the number of active motor units (recruitment) can be derived and was estimated to be 44% (Fig. 2).

CHEST WALL MECHANICS AND RESPIRATORY MUSCLE FUNCTION IN COPD

Chest wall and diaphragm geometry and mechanics are altered in COPD. This has been largely attributed to a passive process due to pulmonary hyperinflation (1). However, the threefold increase in neural inspiratory drive, which is non-uniformly distributed to the synergist inspiratory muscles, is likely to influence remodeling of the chest wall. It has long been accepted that the diaphragm is the principal generator of tidal volume in normal subjects, but the functional capacity of the diaphragm in COPD has only recently been assessed. Studies using chest radiography (89, 98), computer tomography (CT) (18), MRI (100), and ultrasonography (48) have documented that the total diaphragm length is ~25% shorter in patients with COPD than in control subjects at residual volume and ~15% shorter at functional residual capacity (FRC). The...
length of diaphragm fibers vertically oriented in contact with the chest wall [zone of apposition (Lzapp)] in patients with severe COPD was ~50% of that in control subjects at RV and FRC, indicating a dramatic reduction in the reserve capacity to shorten the muscle fibers (48). This must limit the diaphragm’s capacity to generate flow for the same level of neural activation. However, the difference in diaphragm length between COPD and control subjects is relatively small at total lung capacity (TLC), ranging from 7 to 12% in several studies using different methodologies (18, 48, 98). These results are consistent with the concept that the diaphragm may adapt to chronic hyperinflation with a reduction in the number or length of sarcomeres in series (e.g., Ref. 34, 79). The results suggest that relatively little of the increase in lung volume at TLC in COPD is accounted for by shortening of the diaphragm. The diaphragm dome is flatter in patients with COPD compared with control subjects at FRC and RV, but the difference in the ratio of dome height to dome width is <10% (72, 81, 98). However, in patients with COPD, the dome volume changes little during inhalation from RV to TLC, whereas it increases in control subjects (98). Singh and colleagues calculated that flattening of the diaphragm dome contributed ~0.8 liter toward maintaining near normal swept volume in patients with COPD (98). The bulk of the hyperinflation in patients with COPD at RV and FRC is accommodated by shortening of the diaphragm and expansion of the rib cage (18, 48, 98).

Although the diaphragm is shortened in COPD and is therefore operating at suboptimal length, its strength may be preserved. At equivalent absolute lung volumes, the pressure-generating ability of the inspiratory muscles (16, 75) and the diaphragm (94) of COPD patients is equal to or greater than that of control subjects. Nevertheless, it has long been assumed that the functional capacity of the diaphragm in generating volume changes would be reduced in patients with severe COPD (22). Singh and colleagues (98) used posteroanterior (PA) and lateral radiographs at three volumes between FRC and TLC to measure diaphragm length and volume. During inspiration to TLC, the volume displaced by the diaphragm in patients with severe COPD was comparable to that of control subjects. Gorman and colleagues (48) used ultrasonography to measure Lzapp together with measurements of rib cage AP and lateral diameters to estimate diaphragm length continuously during quiet breathing and vital capacity maneuvers using a formula validated in control subjects (81) and patients with COPD (72). Although Lzapp at FRC was reduced by 50% compared with control subjects, the absolute diaphragm shortening during tidal breathing was almost identical for the two groups (~20 mm shortening of Lzapp or ~40 mm shortening of total diaphragm length; Fig. 3). The estimated shortening of diaphragm muscle fibers relative to the total diaphragm length was also not different between the groups (12 vs. 15%). In both groups, 75% of tidal volume was displaced by the diaphragm, even though the mean FRC of the COPD group was equal to their predicted TLC (and similar to the control group’s TLC). There was no correlation between severity of airflow obstruction and diaphragm shortening or volume change during tidal breathing, although the most hyperinflated subjects had the least reserve capacity to shorten the diaphragm. Thus, in tidal breathing, the increased neural drive to the diaphragm elicits a near normal change in swept volume, but, at high lung volumes, the capacity of the diaphragm to change volume is reduced even though its static pressure-generating capacity is preserved. Patients with severe COPD and hyperinflation sometimes exhibit paradoxical indrawing of the lower costal margin during tidal breathing (Hoover’s sign). This phenomenon has traditionally been attributed to contraction of radially oriented diaphragmatic fibers that have peeled away from the chest wall (43, 44). However, ultrasonographic assessment has not documented any patient with COPD in whom the zone of apposition of the diaphragm has reduced to zero before reaching TLC (48). Mean Lzapp at TLC for the group was 3 mm, similar to that for the controls even though 6 of 10 COPD patients had indrawing of the lower costal margin. Multiple linear regression analysis showed that indrawing (Hoover’s sign) was related to high inspiratory drive (as indicated by lower inspiratory time), lower arterial PCO2 (Fig. 4) and worse airway function (low forced expiratory volume in 1 s). The latter result is consistent with the findings of Jubran and Tobin (55) who also found that paradoxical motion was linked to increased airway resistance. Gorman and colleagues (48) also noted that the amount of paradox was not related to reduced diaphragm length or Lzapp at end inspiration. Thus the indrawing must reflect a relatively low subdiaphragmatic abdominal pressure laterally. This could result from sudden relaxation of abdominal muscles at the onset of inspiration and/or strong recruitment of the diaphragm in subjects with limited mechanical capacity for the lower ribs to expand.

The intercostal muscles, possibly because of their complex anatomical and geometric relationships, have been less intensively studied than the diaphragm, but their role in ventilation is important. Activation of the diaphragm in tetraplegic patients leads to paradoxical inward displacement of the cranial half of the rib cage. De Troyer and colleagues demonstrated

Fig. 3. Length of the zone of apposition of the diaphragm in COPD and control subjects. The length of the zone of apposition (Lzapp) for the diaphragm is plotted against lung volume (% predicted total lung capacity [TLC]) for each COPD subject (n = 9; filled symbols) and age-matched control subject (n = 8; open symbols) at TLC (circles), functional residual capacity (FRC; triangles), and residual volume (RV; squares). The lines of best fit are shown for each group of subjects. Although the COPD subjects show a narrower range of Lzapp and lung volume measurements, the relationship between the two variables is similar to control subjects. The lower and upper horizontal dashed lines represent the mean Lzapp length at functional residual capacity for COPD and control subjects, respectively. The mean change in Lzapp (ΔLzapp) during tidal breathing is indicated at right for COPD (21 mm) and control subjects (22 mm) and depicted with shading. [Adapted with permission from Ref. 48, an official journal of the American Thoracic Society, copyright American Thoracic Society.]
that the mechanical advantage (i.e., the change in airway pressure for a change in muscle length) of both the internal and external intercostal muscles depends on the interspace number and the location of the fibers within the interspace (24). Inspiratory action is greatest for the external intercostals in the upper spaces posteriorly and decreases progressively in lower spaces and anteriorly within spaces. Their action is reversed to expiratory in the anterior portion of the lower interspaces. The internal intercostals are predominantly expiratory in the lower chest, but the mechanical advantage decreases progressively in higher interspaces. In the latter spaces, the expiratory action decreases progressively from posterior to anterior, reversing to an inspiratory action for the parasternal intercostals. In a parallel series of experiments, the timing and magnitude of inspiratory neural drive were distributed in proportion to the mechanical advantage of the muscle fibers, both between and within intercostal spaces (13, 23, 37). The close matching between the neural drive and the mechanical advantage of groups of intercostal muscle fibers implies an efficient system, which should minimize the work of breathing (24). However, it is not yet known whether the rostrocaudal and anteroposterior gradients of mechanical advantage and neural drive are altered in COPD. Indirect evidence suggests that the neural drive responsible for these gradients may be “preset” centrally (51).

There is relatively little information about the mechanical properties, function, and adaptation of the intercostal and scalene muscles in COPD. There is no doubt that the rib cage is hyperinflated (as discussed above) with elevation of the ribs and sternum. Therefore, the inspiratory intercostals and scalene muscles must be shortened. However, in both healthy humans and dogs, the paraesternals shorten <10% between FRC and TLC compared with 20–30% for the diaphragm (24). In dogs, the optimal length for tension generation of intercostal muscles is closer to TLC than FRC (32, 52), suggesting that the intercostals may be at a relative advantage compared with the diaphragm in chronic hyperinflation, but these data have been disputed (29). Regardless of the ability of the parasternal muscles to generate tension, the mechanical advantage decreases with hyperinflation and elevation of the sternum (24), whereas compliance of the rib cage decreases. Furthermore, the pressure change generated by a given tension, produced by stimulation of the parasternal muscles in animals, decreases at high lung volumes, due largely to the ribs reaching their limit for outward displacement (59). These issues are reviewed in this mini review series by De Troyer and Wilson (27).

The scalenes are obligatory inspiratory muscles (26), and their neural drive is increased in COPD (38). In dogs, the length change of scalenes during inflation above FRC is relatively small, suggesting that these muscles may retain reasonable mechanical advantage (33). CT scanning has shown that the scalenes of normal subjects shortened ~12% between FRC and TLC compared with only 7% for sternomastoid, confirming its higher mechanical advantage (60). Consistent with these observations, Hudson and colleagues (51) found that scalene activation during slow inspiration from FRC to TLC was 15–40% greater than that of sternomastoid. The ratio of activation of the muscles in Mueller maneuvers at different lung volumes was similar to that during slow inhalation, suggesting a “preset” distribution of neural drive. However, it is not known whether these ratios of mechanical advantage and neural drive apply in patients with COPD. When breathing is shifted to high lung volumes, activity in scalenes increases (51, 87). During graded inspiratory loading, scalene EMG activity correlated with the esophageal pressure time product and with dyspnea rating (19). The sternomastoid is rarely active during resting breathing in patients with COPD, and severe hyperinflation and its contribution as an accessory inspiratory muscle appears questionable other than in tetraplegics (26). In COPD, the sternomastoid is recruited when neural drive is extremely high, such as during weaning from ventilators (101).

The abdominal muscles and other expiratory muscles are often active in patients with COPD and severe hyperinflation, particularly during late expiration (68, 76). This action lengths diaphragmatic muscle fibers just before the onset of inspiration, presumably increasing their ability to generate tension and to shorten. Acute hyperinflation should place the expiratory muscles close to their optimal length for tension generation, but there is little information on the adaptation of these muscles to chronic hyperinflation. It has been suggested that the strength and endurance of expiratory muscles are decreased in COPD (86), but the reasons for this finding are unclear.

**RESPIRATORY MUSCLES IN SLEEP AND EXERCISE**

Despite, or perhaps because of, the chronic increase in drive required to maintain ventilation in COPD, the inspiratory muscles remain relatively resistant to the development of fatigue. There is little evidence that the ultimate development of ventilatory failure is due to peripheral muscle fatigue, with a major mechanism for chronic hypercarbia being a failure to increase central drive sufficient to maintain alveolar ventilation (e.g., Refs. 35, 47, 69, 90, 102). The onset of ventilatory failure is also not tightly linked to the severity of airway narrowing. Among a complex set of physiological disturbances discussed above, individual variations in factors that determine ventilatory control and output to respiratory motoneuron pools (such as chemoreceptor sensitivity) during wakefulness and sleep probably play a role. Sleep is associated with profound changes

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Fig. 4. Change in lateral chest diameter ($\Delta D_L$) during tidal breathing vs. arterial PCO$_2$ for patients with COPD. The regression line ($R = 0.94; P < 0.01$) is plotted for the data excluding the outlier (□), including the outlier ($R = 0.77; P < 0.01$). Patients with indrawing (Hoover’s sign) had lower arterial PCO$_2$. [Reproduced with permission from Ref. 48, an official journal of the American Thoracic Society, copyright American Thoracic Society.]
in respiratory control, neuromuscular function, and lung and chest wall mechanics, many of which are especially deleterious in patients with COPD (73).

Upper airway resistance normally increases during sleep (50), and the risk of upper airway collapse may be exaggerated in COPD because of the increased acceleration of inspiratory flow and pressure. The prevalence of obstructive sleep apnea appears to be higher in COPD than in control populations (11). Resistance of lower airways exhibits a circadian increase in sleep, and this is exaggerated in asthmatics (49). A similar phenomenon might be expected in some COPD patients. These increases in airway resistance are well compensated in healthy individuals but could contribute to decompensation in severe COPD.

Sleep onset is associated with decreased responsiveness of the bulbopontine respiratory neurones to chemoreceptor and other inputs and a marked decrease in facilitatory inputs from the reticular activating system and cortex (e.g., Refs. 10, 82). Ventilation decreases during sleep due to a reduction in tidal volume and decreases further in phasic rapid eye movement (REM) sleep, leading to marked hypoxemia and hypercarbia in patients with severe COPD (30). During REM sleep, there is a reduction in intercostal and scalene EMG with a concomitant increase in diaphragmatic activity and abdominal excursion (53, 103). A reduction in abdominal muscle tone in REM sleep might contribute to the chest wall distortion and the profound decrease in ventilation observed in COPD patients (53).

Other factors contribute to the profound hypoxemia during sleep observed in COPD patients. These include the effect of posture and other sleep-related changes on ventilation-perfusion relationships, the shape of the oxygen dissociation curve, which means that a given decrease in arterial PO2 from a low baseline saturation will result in greater desaturation, and blunted chemoreceptor responses in some patients (73). Thus it is probable that a complex set of sleep-related changes, exaggerated in COPD, results in repetitive or progressive hypoxemia and hypercarbia and contributes to the development of chronic ventilatory failure and cor pulmonale.

Although the diaphragm functions well as a volume generator at rest in COPD, it is compromised during exercise for several reasons. There is usually little reserve capacity for diaphragm shortening at end inspiration. The diaphragm also has little capacity to increase the volume of the lower rib cage because of the degree of hyperinflation of the chest and a reduction in the effect of gastric pressure on the ribcage due to the reduced area of apposition. Airflow limitation and airway closure during deflation mean that patients with COPD cannot increase tidal volume by lowering FRC, which is the normal response to exercise. To increase respiratory frequency entails the risk of dynamic hyperinflation and inspiratory threshold loading further compromising the inspiratory muscles. The development of dynamic hyperinflation is variable, and the patients who maintain FRC have increased activity of abdominal muscles in late expiration (5). This is the normal response to exercise, but in COPD patients it does not increase ventilation because airway closure prevents a decrease in FRC. However, it increases work and oxygen cost of breathing two- or threefold, decreases venous return and cardiac output, and reduces exercise tolerance (1, 3, 4). Thus the diaphragm may be even more compromised by defending FRC than by allowing some dynamic hyperinflation.

During incremental exercise in patients with COPD, the ratio of transdiaphragmatic to total pressure change was higher before than after the onset of inspiratory flow (106). Thus the diaphragm appeared to overcome the threshold inspiratory load imposed by the intrinsic positive end-expiratory pressure before initiation of inspiratory flow (106). Transdiaphragmatic pressure during inspiratory flow did not increase with increasing workload, leading to the suggestion that the ribcage and neck muscles were mainly responsible for developing inspiratory pressures. However, power output of the diaphragm was not measured, so its effectiveness was not revealed. Although transdiaphragmatic pressure rises only modestly during exercise, diaphragmatic EMG increases to near maximal values. This has been taken to indicate a progressive decline in mechanical effectiveness of the diaphragm (77, 96). However, the observed pressure response is similar to that in healthy subjects in whom the diaphragm functions as a low-pressure, high-flow generator (2), and it is probable that the diaphragm retains this function, but in a limited way, in COPD (48, 98).

The high level of activation in the face of high inspiratory loads might be expected to result in diaphragmatic fatigue during exercise. However, the force-generating capacity of the diaphragm is not reduced during exhaustive exercise in COPD patients (67, 84). It is possible that the diaphragm operates close to the threshold for contractile fatigue, as indicated indirectly by a slowing of its relaxation rate (57), with higher workloads inhibited by a metabolic reflex (28).

The preserved strength and fatigue resistance of the diaphragm in patients with COPD may be due to ultrastructural adaptations (e.g., Refs. 62, 78, 85), which are reviewed in the current mini series by Clanton and Levine (20). The diaphragm in COPD patients has a higher percentage of slow (fatigue-resistant) isoforms of myosin heavy chains (MHC-1) and slow light chains, troponins, and tropomysin (62). Mitochondrial oxidative capacity is higher and cross-sectional area lower in all muscle fiber types compared with control subjects, consistent with increased fatigue resistance (63). A reduction in mean sarcomere length has also been documented, pointing to an adaptation to operating at a shorter muscle length (78). More recently, Levine and colleagues (64) reported that the parasternal intercostal also showed evidence of a transformation of fiber types from fast (fatigable) to slow (fatigue-resistant) myosin.

Studies of patients before and after lung volume reduction surgery (LVRS) provide insight into factors that limit exercise in severe hyperinflation due to COPD. Most studies have shown improvements in lung function, exercise capacity, and quality of life. However, the improvements generally show poor correlation with the improvements in airway function. Several studies using different methodologies have documented substantial increases in diaphragm length following LVRS (9, 17, 46). In one report, there was a 30% increase in the length of the zone of apposition of the diaphragm following LVRS, providing a large increase in inspiratory capacity (46). This change in diaphragm length was unrelated to measures of airflow function but closely related to the increase in vital capacity. In these subjects, improvements in exercise capacity and quality of life correlated with increases in diaphragm length and vital capacity. These findings are consistent with a report of improved mechanical efficiency of the diaphragm (volume change per unit pressure change), which persisted for
up to 2 years when improvements in lung function had largely dissipated (58).

Part of the improvement in dyspnea following LVRS relates to reduced neural drive to the inspiratory muscles, presumably due to the increase in diaphragmatic length (46). The discharge frequency of diaphragm and scalene single motor units decreased to a level midway between the patients’ preoperative values and those of control subjects. This would be equivalent to decreasing inspiratory neural drive from threefold to twofold (36).

In conclusion, the hyperinflation of COPD reduces the flow and pressure-generating capacity of the diaphragm. This is compensated by increased neural drive (leading to increased firing rates and recruitment), adaptations of the chest wall and diaphragm shape to accommodate the increased volume, and adaptations of muscle fibers to preserve strength and increase endurance. These limit the impact of hyperinflation on the diaphragm’s ability to generate flow and volume changes. Sleep is associated with profound changes in drive and respiratory function, which are exaggerated in COPD and contribute to the development of cor pulmonale.

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Review

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