Role of the respiratory muscles in acute respiratory failure of COPD: lessons from weaning failure

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1Division of Pulmonary and Critical Care Medicine, Edward Hines Jr. Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine, Hines, Illinois; and 2Medical ICU, AP-HP, Albert Chenevier-Henri Mondor Teaching Hospital, Paris 12 University, INSERM Unit 955, Créteil, France

Submitted 13 February 2009; accepted in final form 29 April 2009

Tobin MJ, Laghi F, Brochard L. Role of the respiratory muscles in acute respiratory failure of COPD: lessons from weaning failure. J Appl Physiol 107: 962–970, 2009. First published April 30, 2009; doi:10.1152/japplphysiol.00165.2009.—It is problematic to withhold therapy in a patient with chronic obstructive pulmonary disease (COPD) who presents with acute respiratory failure so that detailed physiological measurements can be obtained. Accordingly, most information on respiratory muscle activity in patients experiencing acute respiratory failure has been acquired by studying patients who fail a trial of weaning after a period of mechanical ventilation. Such patients experience marked increases in inspiratory muscle load consequent to increases in resistance, elastance, and intrinsic positive end-expiratory pressure. Inspiratory muscle strength is reduced secondary to hyperinflation and possibly direct muscle damage and the release of inflammatory mediators. Most patients recruit both their sternomastoid and expiratory muscles, even though airflow limitation prevents the expiratory muscles from lowering lung volume. Even when acute hypercapnia is present, patients do not exhibit respiratory center depression; instead, voluntary activation of the diaphragm, in absolute terms, is greater in hypercapnic patients than in normocapnic patients. Instead, the major mechanism of acute hypercapnia is the development of rapid shallow breathing. Despite the marked increase in mechanical load and decreased force-generating capacity of the inspiratory muscles, patients do not develop long-lasting muscle fatigue, at least over the period of a failed weaning trial. Although the disease originates within the lung parenchyma, much of the distress faced by patients with COPD, especially during acute respiratory failure, is caused by the burdens imposed on the respiratory muscles.

intrinsic positive end-expiratory pressure; load-capacity imbalance; work of breathing

NEW INSIGHTS into the mechanisms of integrative physiology are usually gained from studies conducted in contrived experimental settings, as with animal models or healthy volunteers or clinically stable patients subjected to imposed challenges. For ethical and logistic reasons, it is very difficult to undertake detailed physiological measurements in a patient who is experiencing acute distress secondary to an exacerbation of chronic obstructive pulmonary disease (COPD). Unfortunately, no animal model provides a realistic representation of an acute exacerbation of COPD. While it is possible to reproduce selected aspects of the pathophysiological picture—for example, imposing inspiratory resistive loads of varying magnitude—in animals or human volunteers, a model that simultaneously incorporates all of the physiological challenges faced by a patient experiencing an acute exacerbation of COPD has not been achieved. Until recently, physiological research in the acute setting had consisted of little more than measurements of arterial blood gases.

A subgroup of patients experiencing exacerbations of COPD develops acute respiratory failure and requires mechanical ventilation. The point at which these patients have recovered sufficiently that discontinuation of mechanical ventilation can be attempted provides the best opportunity for undertaking detailed physiological research under controlled conditions (30–33, 35, 60, 88, 93). Up to half of these patients develop severe distress during the weaning trial and require the resumption of mechanical ventilation. These patients provide an experiment of nature for studying the role of the respiratory muscles in development of acute respiratory failure in COPD. Moreover, the patients who tolerate the weaning trial, and successfully sustain spontaneous ventilation following extubation, provide a control group for comparison.
Research studies in patients with COPD who fail a weaning trial do not serve as an ideal model of acute respiratory failure in COPD. The greatest limitation of the weaning-failure model is the intervening period of mechanical ventilation, during which additional complications may occur. The advantage of the weaning-failure model is that it permits more detailed instrumentation and systematic investigation than is ethically possible in patients who are already in a state of acute respiratory failure when they first reach the hospital. The two conditions, weaning-failure in COPD and acute respiratory failure in COPD, differ from an acute exacerbation of COPD. The latter condition includes a very broad spectrum of disease severity, and most of these patients do not develop acute respiratory failure. As such, the weaning-failure model applies to only a fraction of patients with an acute exacerbation of COPD.

The basic framework for assessing the role of the respiratory muscles in acute respiratory failure in COPD is to group mechanisms under the headings of increased mechanical load, decreased capacity of the respiratory muscles to generate pressure, and the pathophysiological consequences of load-capacity imbalance.

INCREASED LOAD

The most detailed data on the mechanical load experienced by patients with COPD in acute respiratory failure comes from the study by Jubran and Tobin (33) of 31 patients with COPD undergoing a weaning trial. Over the course of a trial of spontaneous breathing, lasting 45 ± 8 min, 17 patients developed acute distress and an increase in arterial PCO2 (P_{aCO2}) (from 45 to 58 mmHg), requiring the reinstitution of mechanical ventilation. The remaining 14 patients tolerated the trial and were successfully extubated; these served as a control group.

At the onset of a weaning trial, inspiratory effort, measured as pressure-time product, was markedly higher than normal, but not significantly different, in weaning-failure and weaning-success patients: 255 ± 59 vs. 158 ± 23 cmH2O•s/min [normal, 94 ± 12 (80)]. At the end of the trial, pressure-time product increased more in the failure patients than in the success patients: 388 ± 68 vs. 205 ± 25 cmH2O•s/min. The increase in effort resulted from worsening of all elements of respiratory mechanics.

At the start of the weaning trial, inspiratory lung resistance was markedly elevated, but not significantly different, in the failure and success patients: 9.0 ± 1.7 vs. 5.3 ± 1.1 cmH2O•l^{-1}•s (33) (Fig. 1). By the end of the trial, resistance increased to 14.8 ± 2.0 cmH2O•l^{-1}•s in the failure patients, but it did not change in the success patients. The mechanism of the progressive increase in inspiratory resistance in the failure patients is not known (33).

Dynamic lung elastance was higher in weaning-failure patients than in weaning-success patients at the start of the trial: 21.2 ± 3.4 vs. 9.9 ± 1.7 cmH2O/I (33) (Fig. 1). At the end of the trial, elastance increased to 34.1 ± 4.0 cmH2O/I in the failure patients and to 14.0 ± 2.0 cmH2O/I in the success patients. The elevated elastance at the start of the trial was probably secondary to frequency dependence of elastance. The mechanism of the progressive increase in elastance over the course of the trial is uncertain, but it may be related to progressive dynamic hyperinflation (88) as discussed below.

Intrinsic positive end-expiratory pressure (PEEPi) was higher in the failure patients than in the success patients at the onset of the trial: 2.0 ± 0.5 vs. 0.7 ± 0.1 cmH2O. By the end of the trial, PEEPi increased to 4.1 ± 0.8 cmH2O in the failure patients and to 1.1 ± 0.2 cmH2O in the success patients (33) (Fig. 1).

The appropriateness of using weaning failure as a physiological model of the mechanical load experienced by patients with COPD in acute respiratory failure has been recently corroborated by Purro and coworkers (65). They studied 16 patients within 24 h of admission to hospital for an acute exacerbation of COPD. Nine patients exhibited acute respiratory acidosis (pH 7.28 ± 0.02) and required noninvasive mechanical ventilation and the remaining seven did not exhibit acidosis (pH 7.39 ± 0.04) and were successfully managed without ventilator assistance. During a brief period of unsupported breathing, inspiratory effort was greater in the patients who required noninvasive ventilation than in those who did not (65). Similar to Jubran and Tobin (33), the increase in effort resulted from worsening of all elements of respiratory mechanics.

The two groups of investigators in the just discussed studies (33, 65) did not partition total PEEPi into the component
resulting from expiratory muscle contraction, and that resulting from an increase in end-expiratory lung volume. We recently obtained this information by assessing patients with COPD who failed a weaning trial (60). We partitioned total PEEPi into that resulting from expiratory muscle contraction (abdominal muscles, expiratory rib-cage muscles, or both; see Expiratory muscles) by calculating the rise in gastric pressure (Pga) between the onset of expiratory flow and the point of rapid decline in esophageal pressure (Pes), and the remaining portion, reflecting an increase in end-expiratory lung volume. After correcting for expiratory-muscle contribution, the remaining portion of total PEEPi, reflecting change in end-expiratory lung volume, increased between the start and end of the weaning trial in 7 of the 10 patients (60). These data suggest that many weaning-failure patients develop dynamic hyperinflation. Expiratory flow limitation (34) and tachypnea, through a decrease in time available of exhalation (84), are the most likely determinants of dynamic hyperinflation. It should be recognized that it has not been possible to obtain direct measurements of end-expiratory lung volume in patients experiencing acute respiratory failure, and the use of esophageal pressure to estimate this entity is based on many assumptions (92).

**Respiratory muscles: function, activity, and neural drive**

**Inspiratory muscles.** Patients with COPD, even when stable, do not generate as much negative maximal inspiratory pressures as do healthy subjects (52, 63), indicating a decrease in respiratory muscle strength. At least two pieces of evidence indicate that the decrease in muscle strength is not the result of decreased muscle recruitment: 1) respiratory muscle recruitment during maximal voluntary efforts is maximal or near maximal (74, 87); and 2) the transdiaphragmatic pressures elicited by phrenic nerve stimulation—a technique that eliminates the influence of the central nervous system—is less than in healthy subjects (82). The decrease in force-generation capacity of the diaphragm could be the result of the greater protein degradation of its fibers (59). In some patients, however, the smaller swings in airway (52) and transdiaphragmatic (63, 74, 86) pressures (10, 11) can be completely explained by hyperinflation-induced muscle shortening.

The mechanisms responsible for impaired force generation by the muscle fibers themselves are discussed by Clanton and Levine in this Highlighted Topic series (12), and the mechanisms whereby hyperinflation impairs respiratory muscle function are discussed in detail by De Troyer and Wilson in this series (19).

In addition to weakness, diaphragmatic myofibers of patients with moderate-to-severe COPD are also more susceptible to sarcomere disruption when subjected to an acute inspiratory load than are the diaphragms of healthy controls (68). This observation has potential clinical implications as suggested by analysis of postmortem specimens from the diaphragms of patients with severe COPD (72). These specimens reveal that acute-on-chronic ventilatory loading induces extensive diaphragmatic injury and collagen accumulation (72).

Circumstantial evidence suggests that increased load, hyperinflation, and inflammatory mediators could be the initial triggers leading to the cellular and molecular changes that contribute to diaphragmatic weakness in COPD (58). In a study of 34 patients with moderate-to-severe COPD, Spruit and coworkers (77) reported increased levels of circulating inflammatory cytokines (IL-6 and IL-8) during an exacerbation although these were not related to maximal inspiratory pressures. Confounding factors, such as administration of steroids (75) to all patients and lack of data on local expression of anabolic factors (16), make it difficult to reach a convincing conclusion about the effect of the increased cytokine levels on respiratory muscle performance.

Patients with COPD have an increased risk of coronary artery disease, and 20–30% have chronic heart failure (42). Increased stress on the myocardium during an exacerbation of COPD or an episode of weaning failure could overwhelm an already impaired cardiac reserve and cause acute left-ventricular failure (31, 44). An increased load resulting from interstitial edema secondary to acute left-ventricular failure together with decreased blood flow to the respiratory muscles may markedly impair respiratory muscle performance and reduce the time to task failure (4).

**Expiratory muscles.** More than half of patients stable with severe COPD actively recruit their transversus abdominis muscle during resting breathing (54). The resulting phasic rise in abdominal pressure contributes to the generation of PEEPi (55).

Insight into the activity of the expiratory muscles in patients with COPD experiencing acute respiratory failure can be gained from a recent study of 19 patients being weaned from mechanical ventilation (60). All but 1 of the 11 weaning-failure patients exhibited expiratory muscle activity (the exception being a patient with paraplegia). Expiratory muscle activity, as quantified by the expiratory rise in Pga, was absent in all but three of eight weaning-success patients, and its magnitude was trivial (Fig. 2). At the onset of the trial, the expiratory rise in Pga was equivalent in the failure and success groups, 0.9 ± 0.5 and 0.1 ± 0.1 cmH2O, respectively (P = 0.3) (Fig. 2). At the end of the trial, the expiratory rise in Pga increased to 4.4 ± 1.1 cmH2O in the failure group (P = 0.0005), whereas it did not change, 0.1 ± 0.1 cmH2O, in the success group (P = 0.4) (Fig. 2). Compared with the success group, the failure group exhibited larger increases in expiratory rise in Pga (P = 0.004). In the failure group, expiratory muscle activity accounted for 53 ± 4% of total PEEPi throughout the weaning trial.

In patients with COPD experiencing acute respiratory failure, heightened activation of the expiratory muscles represents an automatic component of the response of the respiratory system.
We investigated sternomastoid muscle recruitment in patients with COPD experiencing acute respiratory failure by inserting fine-wire electrodes into the sternomastoid muscles of patients undergoing a weaning trial (60). Sternomastoid EMG activity was evident in 83 ± 9% of all the breaths in the weaning-failure group and in 19 ± 10% of all breaths in the weaning-success group (P = 0.002) (Fig. 3). Sternomastoid activity became evident within the first minute of the trial in 8 of the 11 failure patients and 1 of the 8 success patients. By the end of the trial, sternomastoid activity was noted in all failure patients but in only three of the success patients, and even this was modest. The immediate increase in sternomastoid activity in the failure patients probably results from increased drive in response to a combination of decreased capacity of the respiratory muscles to generate pressure (35) and [as we have previously shown (33)] an increase in respiratory load that occurs early during the weaning trial.

A striking feature of the weaning-failure patients is the timing at which different muscle groups become active (60). The sequence begins with activity of the diaphragm and with greater activity of inspiratory rib-cage muscles than is the case in the success patients; recruitment of sternomastoids and rib-cage muscles is near maximum within 4 min of trial commencement; and the expiratory muscles are not recruited until quite late in the trial [at 17–20 min (60)]. The existence of a hierarchy of respiratory muscle activation is supported by the known delayed activation of the sternomastoid muscles (28) and expiratory muscles in healthy volunteers (41, 89) and in ambulatory patients with COPD (15).

CONSEQUENCES OF LOAD-CAPACITY IMBALANCE

Rapid shallow breathing. Patients with COPD who develop acute respiratory failure typically develop an increase in PaCO₂ (9), as do many patients who fail a weaning trial (33). In the past it was thought that the acute increase in PaCO₂ was the result of a decrease in respiratory center output. Several investigators have shown that, in absolute terms, respiratory drive is not depressed in such patients—if anything, respiratory drive is higher in weaning-failure than in weaning-success patients. The high respiratory drive in such patients results in increased

![Fig. 3. Representative tracings of flow, esophageal pressure (Pes), and sternomastoid EMG (EMGscm) in a weaning-failure patient. Recordings were obtained during the first minute of the weaning trial, 40% of trial duration, and last minute of the trial. Phasic inspiratory activity of the sternomastoid muscle was evident within the first minute of the trial, and it increased progressively over the course of the trial. [Reproduced from Parthasarathy et al. (60).]](http://jap.physiology.org/)
swings in transdiaphragmatic pressure. In nine patients with COPD in acute respiratory failure, for example, Brochard et al. (9) recorded transdiaphragmatic pressures of 19 ± 2 (SE) cmH2O. Despite the considerable inspiratory effort, tidal volume was only 289 ± 35 ml in these patients. These values contrast with a transdiaphragmatic pressure of 9 ± 1 cmH2O and a tidal volume of 699 ± 54 ml that we recorded in 15 clinically stable patients with severe COPD who were scheduled for lung-volume reduction surgery (38).

Rather than respiratory center depression, the major mechanism for the acute hypercapnia is a change in the pattern of breathing. Before the institution of (noninvasive) mechanical ventilation, patients experiencing acute respiratory failure consequent to an acute exacerbation exhibit a breathing pattern that is rapid and shallow (9, 43). When patients are disconnected from a ventilator, those who go on to fail a weaning trial develop an almost immediate change in breathing pattern (84). The dominant finding is a shortening of inspiratory time (TI). For example, in the study of Tobin and coworkers (84), TI was 0.8 ± 0.1 s in weaning-failure patients vs. 1.4 ± 0.3 s in weaning-success patients. Within the respiratory centers, expiratory time (TE) is strongly coupled to TI. Consequently, TE was also shorter in the weaning-failure patients than in the weaning-success patients: 1.2 ± 0.3 vs. 2.5 ± 0.5 s. The combined changes in TI and TE led to a marked increase in respiratory frequency: 33 ± 2 vs. 21 ± 3 breaths/min. Because the rate of inspiratory flow [tidal volume (VT)/TI] was equivalent in the two patient groups, the short TI resulted in a lower VT in the failure patients: 194 ± 56 ml. The decrease in VT was balanced by the increase in frequency, and thus minute ventilation (V̇E) was equivalent in the two groups. A decrease in VT without an increase in V̇E must result in higher overall dead space ventilation (VD/VT). An attempt to compensate for the low VT through an increase in frequency will produce an increase in work of breathing. According to the model of Otis et al. (57), the increase in work with rapid shallow breathing is exponential: work = 4,035e^{0.0017f/VT}, r = 0.90 (66, 67) (Fig. 4).

Several groups of investigators have shown that rapid shallow breathing (high frequency, low VT) is a characteristic finding in weaning-failure patients. The degree of rapid shallow breathing can be quantified by calculating the ratio of respiratory frequency to tidal volume (f/VT). The higher the ratio, the more severe is the rapid, shallow breathing. An f/VT ratio of 100 has been shown to be the best predictor of weaning outcome and has become part of routine diagnostic testing in ventilated patients (81). In patients experiencing an acute exacerbation of COPD, a further mechanism that may contribute to the development of hypercapnia is impaired voluntary activation of the diaphragm. Topeli and coworkers (87) investigated this possibility using the twitch interpolation technique in 15 patients with stable COPD. When the phrenic nerves are stimulated during a voluntary contraction, the increase in transdiaphragmatic pressure reflects the proportion of muscle not recruited by voluntary activation. Voluntary activation was higher in the six patients who had hypercapnia than in the nine patients with normocapnia, 95% vs. 89%; the value in normocapnic patients was equivalent to that reported in healthy subjects (88%; Ref. 3). The extent of voluntary activation of the diaphragm and PaCO2 were both positively correlated with inspiratory muscle load (87). The results suggest that, contrary to expectations, development of hypercapnia is not the result of impaired voluntary activation of the diaphragm and that patients with a high load may have learned to fully activate their diaphragm on an intermittent basis (87). The latter explanation is supported by recent data that suggest that suprapontine compensatory mechanisms are active in defending ventilation in awake human subjects challenged with an inspiratory load (69). The ability to mount an increase in voluntary drive to the diaphragm may be especially important during an acute exacerbation of COPD.

Respiratory muscle fatigue. Contractile fatigue occurs when a sufficiently large respiratory load is applied over a sufficiently long period. Contractile fatigue can be brief or prolonged (40). Short-lasting fatigue results from accumulation of inorganic phosphate, failure of the membrane electrical potential to propagate beyond T-tubes, and to a much lesser extent intramuscular acidosis (40). In nine patients who failed a weaning trial (4 of whom had COPD), Brochard et al. (8) reported electromyographic signs suggestive of incipient short-lasting diaphragmatic fatigue. At the point that a reduction in ventilator support led to a shift in the electromyographic power-spectrum, which is suggestive of short-lasting diaphragmatic fatigue, patients started to recruit their sternomastoid muscles. Short-lasting fatigue appears to have a protective function, because it can prevent injury to the sarcolemma caused by forceful muscle contractions (94). Long-lasting fatigue (36) is consistent with the development of, and recovery from, muscle injury (29, 94).

Modest intermittent resistive loading (2 h/day over 4 days) can disrupt sarcomeres and the sarcolemma of diaphragmatic fibers in dogs (95). The sarcolemma disruption involves more type I than type II fibers (95). This mechanism may occur in patients. The proportion of abnormal fibers in the diaphragm was correlated with airflow obstruction in 21 patients with forced expiratory volume in 1 s (FEV1) ranging from 16 to 122% of predicted (50). Abnormalities consisted of myofibers with internally located nuclei, lipofuscin pigmentation (sign of oxidative stress), small angulated fibers, inflammation, and necrosis; these abnormalities occupied 4–34% of the dia-

![Fig. 4. Relationship between work of breathing and the frequency-tidal volume (f/VT) ratio for a constant alveolar ventilation of 4 l/min based on the model of Otis and collaborators (57). Work of breathing is least for f/VT ratios of 37 than 59 breaths·min⁻¹; it increases exponentially as f/VT increases from 59 to 234 breaths·min⁻¹. [Reproduced with permission from Tobin (80a).]
phragm (50). Sarcomere disruption has been reported in 18 patients with COPD (56). The density and area of disruptions in the patients were twice that seen in 11 control subjects, and it was correlated with FEV1 and hyperinflation (56). Diaphragmatic damage has been reported in patients dying of asphyxia, status asthmaticus, or COPD (20, 72), and in infants dying of the sudden infant death syndrome (73).

Patients who fail a weaning trial are at particular risk of developing fatigue because they experience marked increases in respiratory load (33, 64, 88). The addition of a new injury to the respiratory muscles (secondary to the development of contractile fatigue) might be the ultimate determinant of whether or not some patients are ever successfully weaned. Circumstantial evidence of contractile fatigue in patients experiencing respiratory distress has been reported (13, 21, 25, 33). Because of technical limitations (13, 21, 25), these early data did not provide proof of contractile fatigue (82, 85).

To assess whether critically ill patients develop long-lasting fatigue, Laghi and coworkers (35) measured the contractile response of the diaphragm to phrenic nerve stimulation in 16 patients being weaned from mechanical ventilation. The nine patients who failed the trial experienced a greater respiratory load, and as a result of greater neural drive, they developed greater diaphragmatic effort than did the seven weaning-success patients. Not a single patient developed a decrease in transdiaphragmatic twitch pressure elicited by phrenic nerve stimulation. The absence of fatigue was surprising because seven of the nine weaning-failure patients had a tension-time index above the threshold reported to lead to task failure and fatigue (0.15) (6).

One likely reason that patients did not develop fatigue is because physicians re instituted mechanical ventilation before there was enough time for its development. The relationship between tension-time index and the length of time that a load can be sustained until task failure follows an inverse-power function. Bellemare and Grassino (6) expressed the relationship as: time to task failure = 0.1 × (tension-time index)^-3.6. The increase in tension-time index over the course of the weaning trial (35) and predicted time to task failure (6) are shown in Fig. 5. At the point that the physician re instituted mechanical ventilation, patients were predicted to be an average of 13 min away from task failure. Moreover, the time to task failure was underestimated because diaphragmatic recruitment during maximal voluntary contractions was incomplete (35). In other words, patients display clinical manifestations of severe respiratory distress for a substantial time before they would develop fatigue. In an intensive care setting, these clinical signs will lead attendants to reinstitute mechanical ventilation before fatigue has time to develop.

Susceptibility to fatigue is greater when fatiguing protocols are conducted at optimum muscle length rather than when a muscle is shortened (24). Therefore, an increase in dynamic hyperinflation might contribute to the lack of fatigue in weaning-failure patients. Another explanation would be increase in type I fibers (46) in weaning-failure patients. The mechanisms whereby patients with COPD may have increased respiratory muscle endurance (39, 47) are discussed in detail by Clanton and Levine in this series (12).

Studies in animals (1, 53, 67, 71) support the finding that patients do not develop long-lasting contractile fatigue of the respiratory muscles. Inspiratory loading causes respiratory failure and acidosis before force output decreases or substrate is depleted in the diaphragm (1, 53, 67, 71), suggesting that central (17, 79) and reflex mechanisms (27, 76) affect the breathing pattern (66) and α-motoneuron firing rates (51) in response to loading. Two neural pathways may convey information from the respiratory muscles to the central nervous system (17, 62). One pathway transmits information from mechanoreceptors [Golgi tendon organs and muscle spindles (27, 49)] in the dorsal column, relaying it to the brain stem and thalamus, before reaching the sensorimotor cortex (17, 96). This pathway may participate in proprioceptive control of the respiratory muscles, integrating movements originating in the motor cortex (79). The second pathway consists of vagal (1, 17) and possibly phrenic nerve afferents [group IV phrenic afferent fibers (27)] that reach the amygdala after relaying in the brain stem and then projecting to the mesocortex [cingulated gyrus (17)]. This pathway may deal with respiratory nociception (14, 79), such as dyspnea [through the relay in the amygdala (7)], and the ventilatory response to carbon dioxide [through the relay in the brain stem, ventral cerebellum, and limbic system (26)] (14, 79). In addition to these two pathways projecting to the central nervous system, there is evidence for the existence of a spinal pathway responsible for phrenic-to-phrenic reflex inhibition (76). The net effect of these reflex pathways may

Fig. 5. Interrelationship between the duration of a spontaneous breathing trial, tension-time index of the diaphragm, and predicted time to task failure in 9 patients who failed a trial of weaning from mechanical ventilation. The patients breathed spontaneously for an average of 44 min before a physician terminated the trial. At the start of the trial, the tension-time index was 0.17, and the formula of Bellemare and Grassino (6) (see text for details) predicted that patients could sustain spontaneous breathing for another 59 min before developing task failure. As the trial progressed, the tension-time index increased, and the predicted time to development of task failure decreased. At the end of the trial, the tension-time index reached 0.26. That patients were predicted to sustain spontaneous breathing for another 13 min before developing task failure clarifies why patients did not develop a decrease in diaphragmatic twitch pressure. In other words, physicians interrupted the trial on the basis of clinical manifestations of respiratory distress, before patients had sufficient time to develop contractile fatigue. [Reproduced from Laghi and Tobin (40) from an official journal of the American Thoracic Society, with permission. Copyright American Thoracic Society.]
be to inhibit the inspiratory muscles in the face of potentially fatiguing loads, thereby protecting them from irreversible damage, at the cost of CO₂ retention. Finally, an increase in CO₂ during loading may also protect the respiratory muscles by decreasing production of reactive oxygen species (78).

Mechanical ventilation. Levine and coworkers (48) have recently published data showing that mechanically ventilated patients are at risk of an additional mechanism of respiratory muscle weakness: muscle atrophy (83).

They obtained biopsies of the costal diaphragms from 14 brain-dead organ donors (48). These patients exhibited diaphragmatic inactivity and had received mechanical ventilation for 18–69 h. They also obtained intraoperative biopsies of the diaphragms of eight patients undergoing thoracic surgery for suspected lung cancer; these control patients had experienced diaphragmatic inactivity and mechanical ventilation for 2–3 h. Histologic measurements revealed marked diaphragmatic atrophy in the brain-dead patients. Compared with the control group, the mean cross-sectional areas of muscle fibers were significantly decreased by more than 50%. The cross-sectional area of fibers of the pectoralis major, a muscle not affected by mechanical ventilation, was equivalent in the two groups. This finding indicates that the diaphragmatic atrophy experienced by the brain-dead patients was not part of some generalized muscle-wasting disorder.

Biochemical and gene-expression studies suggest that the atrophy resulted from oxidative stress leading to muscle protein degradation. Evidence of oxidative stress is indicated by a 23% lower concentration of glutathione in the diaphragms of brain-dead patients than in the controls. A critical step in muscle proteolysis is the dissociation of proteins from the myofibrillar lattice, which can result from the action of caspase. Expression of active caspase-3 was 154% higher in the brain-dead patients than in the controls. Muscle proteolysis typically involves the ubiquitin-proteasome pathway, including the action of the ubiquitin ligases, atrogin-1 and muscle ring finger-1 (MuRF-1). The number of mRNA transcripts for atrogin-1 and MuRF-1 were 200% and 590% higher, respectively, in the brain-dead patients than in the controls. Based on these findings, Levine and coworkers (48) concluded that 18–69 h of complete diaphragmatic inactivity and mechanical ventilation produced marked diaphragmatic atrophy as a result of increased oxidative stress leading to activation of protein degradation pathways. Physiological correlates of the morphological and biochemical findings of Levine and coworkers (48) are yet lacking.

CONCLUSION

With every research study, the goal of investigators is to formulate generalizations based on collected data (70). The merging and averaging of data tend to cancel out random variation among individual subjects. When a clinician faces a patient with COPD who has developed acute respiratory failure or weaning failure, however, he or she has to diagnose the most likely cause in that particular patient. Most patients with COPD develop acute respiratory failure because of excessive mechanical load, insufficient respiratory muscle strength, or a combination of the two (33, 35). Jubran and Tobin (33) observed that 2 of 17 (12%) weaning-failure patients developed PaCO₂ values of >70 mmHg during a weaning trial, and yet detailed measurements of their lung mechanics and respiratory muscle function were within the range of the weaning-success patients. In these patients, depressed respiratory center output was probably the dominant reason for acute hypercapnia, although most patients in acute respiratory failure exhibit an elevated respiratory center output. Some patients exhibit only mild cardiopulmonary derangement but complain of severe dyspnea; these patients may have heightened afferent responses to sensory stimulation or a problem in how the insula processes the signals (5). In sum, multiple mechanisms, some canceling out another, produce the average picture, yet a single mechanism may dominate in an individual patient. This pattern differs from a laboratory experiment, where investigators control multiple variables to elucidate the contribution of a single factor. Experiments of nature may be handicapped by confounding variables, but the investigators have the advantage of being certain that the process they are investigating is precisely what they set out to investigate.

Understanding of acute respiratory failure in COPD is limited by many unknowns. We have a good understanding of how hyperinflation interferes with respiratory muscle function (19), yet we have no method that reliably measures changes in end-expiratory lung volume in severely ill patients. We also need research into the different forms of dyspnea in patients experiencing acute respiratory failure, the role of high-frequency fatigue, the influence of different forms of patient-ventilator asynchrony on weaning success, and the benefit of pharmacological agents (for example, effect of antioxidants on respiratory muscle function or cardiac inotropes).

GRANTS

This research was supported by a Merit Review Grant from the Department of Veterans Affairs Research Service.

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