Therapeutic Considerations in Respiratory Muscle Function

John T. Sharp, M.D., F.C.C.P.*

Inspiratory muscle function is impaired in many patients with severe COPD. This functional impairment often leads to hypercapnic respiratory failure via inspiratory muscle fatigue. Factors responsible for this functional impairment are: (1) an excessive mechanical load (high resistance and low compliance) for the inspiratory muscles to overcome; (2) the low, flat configuration of the diaphragm owing to lung hyperinflation; (3) reduced inspiratory muscle blood flow relative to the increased respiratory work requirement; and (4) tachypnea which increases the duty cycle (T/t) for inspiratory muscles, increases hyperinflation, wastes ventilation, and otherwise causes deterioration of gas exchange.

Therapy is directed toward improving inspiratory muscle function and has three strategic goals: (1) to reduce the load imposed on the inspiratory muscles and reduce their mechanical disadvantage; (2) to improve the contractile characteristics of the inspiratory muscles; and (3) if goals 1 and 2 cannot be attained otherwise, to rest the inspiratory muscles using mechanical ventilation. Inspiratory muscle training offers promise as a means of preventing hypercapnic respiratory failure. Available data suggest that some COPD patients benefit from it. To be determined are which patients will benefit from it and which will not, as well as which training regimens are most effective.

My task is to discuss therapy in chronic obstructive pulmonary disease (COPD), with particular emphasis on how respiratory muscle function may be improved. To approach this aspect of therapy rationally, a few fundamental concepts concerning skeletal muscles in general and respiratory muscles in particular will be reviewed.

It is the inspiratory muscles rather than the expiratory muscles which are stressed often to the point of fatigue and failure in COPD. There are several reasons why inspiratory muscle function may deteriorate, the major one being related to lung hyperinflation and the low, flat configuration of the diaphragm often seen in severe emphysema. Individual muscle fibers in the diaphragm are shortened in the presence of hyperinflation and are incapable of generating tension optimally. This effect is a reflection of the well-known length-tension or force-length characteristics of skeletal muscle. Although there is evidence that diaphragmatic fibers may shorten their optimal lengths under these circumstances by sarcomere absorption (much as women's calf muscles may shorten in response to constantly wearing high-heeled shoes), this compensatory shortening, if it occurs in clinical COPD, is probably not sufficient to be fully compensatory. To some degree other inspiratory muscles, such as the external and parasternal intercostals, the scaleni, and the sternomastoids, are probably also over-shortened and their tension-generating ability compromised by hyperinflation.

The flat shape assumed by the diaphragm in severe hyperinflation is also a factor in reducing its effectiveness as a pressure generator. Because the diaphragm takes the form of a curved surface, Laplace's law applies to it and determines the relationship among transdiaphragmatic pressure (ΔP_d), tangential tension (T_d), and the diaphragm's effective radius (or radii) of curvature (r). The law states that

ΔP_d = \frac{T_d}{r}

A flat diaphragm means that the radius of curvature, r, is large, and hence, for a given tension generated by the diaphragm's fibers, the transdiaphragmatic pressure will be reduced. In the extreme situation of a completely flat planar diaphragm, the muscle could generate no transdiaphragmatic pressure and would have no inspiratory action. Indeed, if it could contract at all, it would pull the lower rib margins inward and so have an expiratory rather than inspiratory action.

At large lung volumes, the combination of fiber shortening (involving all the inspiratory muscles) and curvature change (involving the diaphragm) results in reduction in the maximum pressure which the diaphragm and the other inspiratory muscles can generate. This was first pointed out by Rahn et al10 in their classic 1946 paper. These investigators also looked at maximal expiratory pressures and showed that, in contrast to the inspiratory muscles, the expiratory muscles function most effectively at large lung volumes. Hyperinflation would not be expected to impair the function of the expiratory muscles in the way it does that of the inspiratory muscles. Additionally, it is

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accepted that expiratory air flow is limited by dynamic collapse of airways and not by mechanical contractile properties of the respiratory muscles, as is the case with inspiratory air flow.

Another factor contributing to inadequacy of inspiratory muscle function in severe COPD is the increased mechanical impedance or load offered by the respiratory system. Inspiratory airway resistance is often increased several-fold, and effective (dynamic) lung compliance is often reduced to a fraction of the normal value. Consequently, the inspiratory muscles must bear a load several times normal at a reduced mechanical advantage caused by hyperinflation. When this unfortunate combination becomes extreme, inspiratory muscle fatigue and failure can result.

Yet another property of inspiratory muscles important in determining their function is their metabolic behavior. Most skeletal muscles are a mixture of three basic muscle fiber types, fast oxidative glycolytic (FOG), fast glycolytic (FG), and slow oxidative (SO). FOG and SO fibers are fatigue resistant and have greater endurance than FG fibers which are fatigue prone. The fiber composition of the three principal inspiratory muscles is shown in Table 1. All three contain 75 percent or more of fatigue-resistant, high-endurance fibers.7 This is appropriate for muscles which must function constantly for a lifetime with no protracted period of rest. However, resistance to fatigue depends on the muscle’s receiving a constant, continuous supply of metabolic substrates and oxygen via the circulation. The blood flow requirements of the muscle increase as its mechanical workload increases. If cor pulmonale and right heart failure lower the cardiac output, this may in turn reduce diaphragmatic blood flow. If delivery of oxygen and metabolic substrates to the muscle via its blood flow falls below the muscle’s metabolic needs, muscle fatigue and failure will soon develop. Acidosis within muscle fibers resulting from anaerobic metabolism will further reduce the muscle’s contractility.8 In two animal models of hypercapnic respiratory failure, that due to cardiogenic shock and that associated with septic shock, low diaphragmatic blood flow and intracellular acidosis have been shown to be of major importance.8,10

Table 1—Fiber Composition of the Major Primary Respiratory Muscles*

<table>
<thead>
<tr>
<th>Muscle</th>
<th>FG (IIB), %</th>
<th>FOG (IIA), %</th>
<th>SO (I), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphragm</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Intercostals</td>
<td>21</td>
<td>26</td>
<td>53</td>
</tr>
<tr>
<td>Scaleni</td>
<td>17</td>
<td>23</td>
<td>60</td>
</tr>
</tbody>
</table>

*From McKenzie DK, et al;12 FG = fast glycolytic; FOG = fast oxidative glycolytic; SO = slow oxidative.

aries are compressed and blood flow slows markedly or even ceases. Thus, the vigorously contracting inspiratory muscles in the COPD patient often function under metabolic and circulatory as well as mechanical disadvantages.

In the development of inspiratory muscle fatigue, a time factor is involved. Since the inspiratory muscles contract rhythmically over a lifetime and since they must "pay as they go" (they cannot "go now and pay later"), they must have time to recover after each inspiration. For this reason the relationship of contraction time to recovery time is important in determining whether muscle fatigue and failure will occur. In this regard the time factor is of comparable importance to the magnitude of the load and the adequacy of substrate and oxygen delivery.

Recently, Bellemare and Grassino14,15 put the load and time factors together and resurrected the concept of the time-tension index, an idea first proposed by cardiovascular physiologists a generation ago. They expressed the time factor as the duty cycle, that is, the ratio of inspiratory time to total respiratory cycle time, or T/Tw. The load factor they expressed as the tension or pressure required for a given repetitive respiratory task (such as breathing through a resistance) divided by the maximal tension or pressure that the subject could generate under comparable conditions. In dealing with the diaphragm in man, this factor was transdiaphragmatic pressure required for the task divided by maximal transdiaphragmatic pressure at the same lung volume, or the ratio Pd/Pd max. Consequently, the time-tension index for the diaphragm could be expressed as (T/Tw) × (Pd/Pd max). Using inspiratory loading experiments on normal subjects, Bellemare and Grassino determined that the critical value for the time-tension index was about 0.15. This is to say, when the time-tension product exceeded 0.15, fatigue of the diaphragm would eventually develop. If the value remained below the critical value of 0.15, the subject could perform the respiratory task indefinitely without developing diaphragmatic fatigue and failure. Subsequent work by the same authors in patients with COPD suggested that the critical time-tension index value of 0.15 was probably valid for such patients.15

Next, it is acknowledged that patients with hypercapnic respiratory failure breathe much faster than they ought to.14 Analyses of the theoretically optimal respiratory rate in small animals and normal man, and the projection of the resulting principles to COPD patients indicate that they would breathe more efficiently from both mechanical and gas exchange (VE/VE) considerations if they breathed at rather slow rates.16,17 However, contrary to what would seem to be their best interests, these patients breathe quite rapidly, particularly when acute events are superimposed on a stable background of mild-to-moderate
chronic hypercapnia. Figure 1 shows arterial blood gas and respiratory rate data on a hypothetical patient who has an event precipitating acute hypercapnic failure. After the precipitating events, his blood gases deteriorate synchronously with the development of tachypnea. With treatment and time, the blood gases improve, and the respiratory rate returns to values present before the precipitating event.

Tachypnea has at least three detrimental effects on respiratory muscle performance and, of course, also makes gas exchange less efficient and adversely stresses a system in which unequal time constants of terminal airway-alveolus units exist. First, as anyone who has done a maximum breathing capacity evaluation (MBC) in a COPD patient can confirm, tachypnea causes increased air trapping, further increasing hyperinflation and aggravating the effects of hyperinflation on inspiratory muscle fiber length and diaphragmatic curvature. Second, during tachypnea, the total respiratory cycle is often shortened to a greater extent

**Figure 2.** A scheme for the pathogenesis of hypercapnic respiratory failure in patient with COPD. See discussion in text.
than the inspiration time, increasing the duty cycle, $T_i/T_{\text{tot}}$. Third, because tachypnea increases the ratio of dead space ventilation to minute volume ($V_D/V_E$), tachypnea increases disproportionately the amount of total ventilation ($V_E$) required to sustain a given level of alveolar ventilation and to maintain a given alveolar and arterial $P_{CO_2}$. The increased ventilation requires more respiratory work and greater respiratory pressures, including transdiaphragmatic pressure ($P_{di}$).

In view of the pivotal importance of tachypnea in this clinical situation, the critical question seems to be "What causes the tachypnea?" The stimulation of lung and airway receptors had been advanced as an explanation, which may well be the answer. An attempt in man to reverse the tachypnea by topical anesthesia failed to do so by more than a slight degree and actually worsened arterial blood gases. However, this is a difficult if not impossible experiment to do properly in man, and it is only fair to say that the question has not been adequately explored to date.

Figure 2 attempts to pull all of this together in a coherent scheme. It also illuminates at least three positive feedback cycles ("vicious cycles"), which substantially aggravate the situation, and suggests that "opening the loops" might be an effective therapeutic strategy.

We begin with three primary observations which can regularly be made in acute hypercapnic respiratory failure: increased mechanical load for the inspiratory muscles, lung hyperinflation, and tachypnea. These features are arrayed horizontally near the top of the figure. The increased mechanical load, due to increased lung resistance and decreased lung compliance, require that greater than normal respiratory pressures be developed, represented by an increased $P_a$. Lung hyperinflation reduces the effectiveness of the inspiratory muscles, reducing the maximal pressure which they are capable of generating, represented by a reduced $P_{a\max}$. When we combine the effect of the increased mechanical load (increased $P_a$) with the effect of hyperinflation (decreased $P_{a\max}$), the net result is a greatly increased ratio $P_a/P_{di\max}$.

Although tachypnea tends to increase the $T_i/T_{\text{tot}}$ ratio, this ratio also may be increased by the high inspiratory resistance, which requires a longer time for a given gas volume to transverse it. Consequently, the combined effect of the increased load, the hyperinflation, and the tachypnea is to increase both terms of the time-tension index. If the time-tension index exceeds the critical value of 0.15, inspiratory muscle fatigue develops. This eventually causes minute ventilation ($V_E$) to decrease, which in turn decreases alveolar ventilation and causes worsening hypoxia and hypercapnia.

The worsening hypercapnia and hypoxia worsen the pulmonary hypertension, often reducing the cardiac output and leading to right ventricular failure. The resulting decrease in systemic blood flow may limit the blood flow to the diaphragm and other inspiratory muscles, compromising their function and further reducing the $P_{di\max}$. This in turn causes a further increase in the $P_a/P_{di\max}$ ratio. This is vicious cycle No. 1.

The tachypnea initiates the second and third vicious cycles as follows. Because tachypnea wastes ventilation ($V_D$ is disproportionately increased), minute volume, $V_E$, must be further increased requiring more respiratory work and greater swings of respiratory driving pressures, including $P_a$. This increases the $P_a/P_{di\max}$ further. This is vicious cycle No. 2.

The tachypnea, by making gas exchange less efficient, leads eventually to yet further worsening of hypoxia and hypercapnia, which ultimately reduces $P_{a\max}$ via vicious cycle No. 1. This is vicious cycle No. 3.

Knowledge of the pathophysiologic processes leading to hypercapnic respiratory failure suggests three basic therapeutic strategies that have proved to be effective in treating this entity. As listed in Table 2, these are: (1) reduce the load which the inspiratory muscles must overcome; (2) strengthen the inspiratory muscles; and (3) if the first two strategies do not work, rest the inspiratory muscles and allow them to recover.

Measures for reducing the load borne by the inspiratory muscles include use of bronchodilator medications and anti-inflammatory drugs, mechanical and medicinal help in clearing the airways of secretions, controlling lung and airway infection with antimicrobial agents, and reducing the body's ventilatory and oxygen needs by controlling fever and keeping carbohydrate intake relatively low. Reducing airway resistance has the additional benefit of decreasing lung resistance, Table 2—Therapy of Hypercapnic Respiratory Failure in COPD in Relation to Inspiratory Muscle Dysfunction

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce the load to the inspiratory muscles</td>
<td>and reduce their mechanical disadvantage</td>
</tr>
<tr>
<td>Reduce airway resistance</td>
<td></td>
</tr>
<tr>
<td>Increase lung compliance</td>
<td></td>
</tr>
<tr>
<td>Reduce hyperinflation</td>
<td></td>
</tr>
<tr>
<td>Reduce ventilatory requirements</td>
<td></td>
</tr>
<tr>
<td>Control infection and fever</td>
<td></td>
</tr>
<tr>
<td>Avoid high-carbohydrate intake</td>
<td></td>
</tr>
<tr>
<td>Strengthen inspiratory muscles</td>
<td>(improve their contractility and endurance)</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td></td>
</tr>
<tr>
<td>Reduce acidosis</td>
<td></td>
</tr>
<tr>
<td>Increase cardiac output and blood flow to</td>
<td></td>
</tr>
<tr>
<td>respiratory muscles</td>
<td></td>
</tr>
<tr>
<td>Drugs that increase respiratory muscle</td>
<td></td>
</tr>
<tr>
<td>contractility</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
</tr>
<tr>
<td>$\beta$-Adrenergic agonists</td>
<td></td>
</tr>
<tr>
<td>Avoid drugs that depress respiratory muscle</td>
<td></td>
</tr>
<tr>
<td>contractility</td>
<td></td>
</tr>
<tr>
<td>If the above do not work, rest the</td>
<td></td>
</tr>
<tr>
<td>respiratory muscles using mechanical</td>
<td></td>
</tr>
<tr>
<td>ventilation</td>
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</table>
hyperinflation.

Measures that strengthen the inspiratory muscles and increase their endurance include oxygen therapy, control of acidosis, interventions that sustain or increase cardiac output and blood flow to the inspiratory muscles, medications that increase respiratory muscle contractility such as theophylline, caffeine, and β-agonists, and, finally, avoiding drugs that might have a damaging effect on contractility.

Finally, if these measures do not work, the inspiratory muscles should be rested by taking over their function using mechanical ventilators. Because of time and space restraints, we cannot here discuss whether complete respiratory muscle rest via the assist-control mode or partial rest via the IMV mode is more effective, although cogent physiologic arguments may be made in favor of either mode.

Since hypercapnic respiratory failure is not an easy entity to treat once it is established, attention has been directed toward prevention in patients with COPD. Other than preventing the occurrence or worsening of the disease by curbing cigarette smoking, the most promising preventive measure in patients already disabled is inspiratory muscle training. Faulkner pointed out that three principles are involved in muscle training: overload, specificity and reversibility. Overload implies that to train a muscle and improve its performance, the training experience must represent a stress greater than that customarily borne by the muscle(s) in question, ie, an overload. Specificity refers to the fact that muscles may be trained for specific characteristics and that the training experience must be tailored to fit the characteristics to be improved. For instance, a weight lifter trains by lifting ever-increasing weights; a marathon runner, on the other hand, trains by running ever-increasing distances with increasing speed. Reversibility means that if the training experience ends, the muscle becomes gradually detrained, reverting back to its pretraining condition: “use it or lose it.” These features should be remembered in discussing the training of respiratory muscles to improve their function in obstructive lung disease.

For the following reasons, it makes more sense to train the inspiratory rather than the expiratory muscles: (1) the inspiratory muscles are laboring under the mechanical disadvantage of a short fiber length and, for the diaphragm, an increased radius of curvature; (2) for the inspiratory muscles, particularly the diaphragm, that show objective evidence of fatigue in ventilatory failure. Recall that in hyperinflation the expiratory muscles, rather than being overly shortened, are at favorable operating lengths or possibly even overstretched. In addition, expiratory flow is limited by airway collapse, and no amount of expiratory muscle strength or endurance is apt to improve expiratory flow.

As to whether strength training or endurance training would be more appropriate, improvement in both characteristics would be desirable. Increased strength would be useful, because inspiratory muscles must generate increased force to overcome increased airway resistance. Increased endurance would be helpful, since it might delay or prevent inspiratory muscle fatigue, thought to be the underlying mechanism for hypercapnic respiratory failure.

Two training maneuvers used thus far are isocapnic hyperventilation and inspiratory resistance breathing. Studies in patients with cystic fibrosis, employing isocapnic hyperventilation, showed that specific respiratory muscle training and general physical training had equally beneficial effects on ventilatory muscle endurance. In quadriplegic patients, similar studies showed that inspiratory resistance breathing just enough to cause electromyographic evidence of diaphragmatic fatigue, done for 30 minutes daily, improved both strength and endurance of the diaphragm. When isocapnic hyperventilation was used in patients with COPD, the training increased maximal sustainable ventilatory capacity, exercise oxygen uptake, maximal exercise ventilation, and exercise performance as assessed by the 12-minute walk.

In another study COPD patients who trained with inspiratory resistance, breathing for 15 minutes twice daily for periods of one and two months, showed enhanced inspiratory muscle endurance but no change in inspiratory muscle strength. The same authors found that general exercise training was less effective than inspiratory muscle training in improving total exercise performance. Finally, training with isocapnic hyperventilation has been reported to facilitate the weaning of patients with COPD and hypercapnic respiratory failure from mechanical ventilation.

Reviewing the recent work on inspiratory muscle training, it is clear that in normal subjects respiratory muscles can be trained, and when training is accomplished, strength, endurance, or both may be improved. The picture is less clear in COPD, particularly in severely disabled patients. Several of the studies thus far reported are not as well designed or controlled as they could be, and the numbers of patients are small. One should remember that the training maneuvers, representing excessive stresses, are capable of injuring muscles as well as improving their function. We need to know which patients are most apt to improve with inspiratory muscle training and which are likely to deteriorate. We need also to determine the best training regimens for patients of different types and severities of disabling airway disease. Clearly, much more clinical research remains to be done in this area.

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DISCUSSION

Dr. Sackner: Some time ago you published a report on the postural relief of dyspnea with different body attitudes. How does change in body posture alter the geometry of the diaphragm?

Dr. Sharp: It has been known for at least 30 or so years that patients with COPD, particularly those who are severely hyperinflated, obtain relief from their dyspnea by bending forward and there are a few in whom relief is achieved by lying down. What we did was to simply try to show that at least one factor in this is diaphragmatic muscle shortening. We observed that when the patient bends forward or is supine, there is less use of the accessory muscles. The ratio of diaphragmatic EMG to pressure generated by the diaphragm is a more favorable one with the patient bending forward or supine than when he is sitting or standing straight up. This suggests that some means of chronically compressing the abdomen might be useful. We have tried this in several patients with belts to constrict the abdomen, but the results have not been too promising.

We have studied abdominal belts to acutely alter transdiaphragmatic pressures and found that it produces short-run benefits. There is some evidence that the diaphragm is working a little more effectively, but in the long run, patients don't wear the belts for any period of time. You send them home with a belt and they return to the clinic without it on. You ask them why, and they reply that after a few days it doesn't seem helpful. Furthermore, they have some trouble eating with the belt on. We intend to explore the use of some sort of belt, possibly inflatable, where the patient can regulate the amount of pressure depending on activity.