Clinical Intervention in Chronic Respiratory Failure

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Despite the obvious partnership of the lungs and the respiratory muscles in ventilation and gas exchange, only within the past 10 years has the possible contribution of the respiratory muscles to chronic respiratory failure been investigated in any detail. The opinion has been challenged that the respiratory muscles, albeit a vital pump, are not immune to fatigue. Increase in the elastic and resistive impedance to breathing in chronic obstructive pulmonary disease (COPD) requires greater force generation by the respiratory muscles. Changes in the elastic properties of the lungs and the prolonged time constant for emptying cause hyperinflation, which puts the inspiratory muscles at a disadvantage. The problems of force generation by the inspiratory muscles are compounded by malnutrition, which can adversely affect ventilatory muscle performance. Knowing these things, respiratory physicians have attempted with mixed success to improve the ventilatory muscles by training, resting, and feeding, where appropriate, of patients with COPD. Implicit in these interventions is the notion that ventilation may be improved at rest or on exertion, or that the intensity of dyspnea may be modified by altered inspiratory muscle function. I will review the basis for such therapeutic approaches and explore some of the possible reasons why we have not witnessed a more significant impact on the functioning of patients with COPD.

INSPIRATORY MUSCLE TRAINING

The performance of certain ventilatory tasks by normal subjects can be improved by training of the inspiratory muscles. Because the exercise capacity of patients with COPD is ventilatory-limited, it is reasonable to postulate that their exercise performance may be improved by appropriate training of the ventilatory muscles. A number of investigators have confirmed that inspiratory muscle training (IMT) can improve inspiratory muscle performance in patients with COPD, which in some cases is also accompanied by improvement in exercise performance. An important question concerning the relationship between IMT and improved exercise performance that has not been satisfactorily answered is the mechanism of the improvement. Is the improved exercise performance a direct consequence of IMT?

Certain arguments can be offered in favor of the link between improvements in exercise performance and inspiratory muscle function. In all of the studies, subjects after training were capable of either tolerating higher resistive loads to inspiration or sustaining higher levels of voluntary ventilation for longer periods, indicating that a specific training effect had been achieved. Even if objective tests of inspiratory muscle performance were not used, part of the training response seems likely to be a peripheral adaptive response. It seems reasonable to assume that changes in the regenerative or metabolic capacity of the inspiratory muscles can be induced by training. Studies of experimental animals indicate a substantial capacity of the respiratory muscles, specifically the diaphragm, to adapt to loading. The observed improvements in exercise performance are therefore associated with, and perhaps also related to, an effect on the inspiratory muscles. However, despite apparent training of the inspiratory muscles, not all subjects with COPD respond to training with improved exercise performance. Pardy et al. reported that the subjects who improved exercise performance after IMT were those who demonstrated electromyographic (EMG) evidence of incipient diaphragmatic fatigue during exercise, suggesting that EMG analysis might predict the likelihood of benefit. In contrast, training-induced improvements in respiratory muscle performance in patients with cystic fibrosis using a similar training protocol were not accompanied by greater exercise capacity, despite a high prevalence (70%) of EMG evidence of fatigue of one or more inspiratory muscles during exercise. The predictive value of the EMG in identifying patients who might improve from IMT was therefore not confirmed.

It has been suggested that some of the inconsistencies in study findings might be related to the fact that control of the training stimulus has been poor, because highly nonlinear flow-resistive devices were most frequently used. Such devices are very sensitive to changes in breathing pattern. To overcome this problem Larson and colleagues used a threshold loading device. Increases in inspiratory muscle strength and endurance were observed when an adequate load was employed, and a significant improvement in exercise capacity was also detectable. Significant improvements in ventilatory muscle strength and endurance have also been shown, using a resistive load and a target feedback device to control the breathing strategy.

Can clinically significant improvements in symptomatology be achieved by IMT? At present, it is difficult to answer this question because it is not clear that the appropriate tools have been applied for evaluation of improvements with training. The problem can be illustrated as follows. Pardy et al. have shown, at least in some subjects, substantial changes in the endurance time on cycle ergometry at an exercise intensity equivalent to 70% of the peak oxygen uptake. In contrast, the distance walked in 12 minutes was improved only slightly (15%, approximately). The discrepancy between tests may not simply be a reflection on the ability of the 12-minute walk test to correctly evaluate performance but may indicate that the limits to exercise are different under the two circumstances. Which outcome is of greater interest clinically? It is probable that the 12-minute walk test is a better reflection of the degree of dyspnea and limitation usually experienced by patients with respiratory failure in their daily lives. Interestingly, despite greater attention to control of the training stimulus, which achieved a 2-fold

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increase in inspiratory muscle endurance, Larson et al also found only a disappointing 8% increase in the 12-minute walk test.

Responses to training are specific to the type of training.15 Endurance training increases endurance and strength training strength. What is the appropriate stimulus to training the inspiratory muscles of patients with chronic respiratory failure for exercise? Perhaps the absence of a change in exercise tolerance to training the inspiratory muscles in certain subjects is caused by the fact that the training stimulus is not entirely appropriate to the strategy of breathing used during exercise. Indirect support for this notion is found in a recent report that inspiratory resistive breathing elicited EMG changes of fatigue and caused a fall in transdiaphragmatic pressure in COPD patients, whereas exercise of comparable intensity, at least in terms of dysnea, failed to demonstrate any such changes.16 It is possible that the training stimulus used by Pardy et al17 was such that it caused training of specific fiber types that are not usually recruited at rest or during low-intensity exercise such as the 12-minute walk test. The training stimulus for improvement in inspiratory muscle function during high-intensity exercise is unlikely to be the appropriate one for submaximal exercise or even less so for breathing at rest.

Perhaps the most serious criticism that can be raised against all of the studies of IMT and exercise performance is the lack of randomization and appropriate controls. Most therapeutic interventions have a certain success rate or placebo effect that may be unrelated to the hypothetical physiologic effect of the interventions. Self-selection for trials of rehabilitation is likely to accentuate the problem. Randomization is designed to avoid such bias and to ensure that sham and experimental groups are comparable. The purpose of controls is to ensure that the experimental and sham groups are treated identically with the exception of the specific intervention. Blinding of subjects as to treatment group is also particularly important in view of the subjective measures used to evaluate treatment effect. Even though IMT achieved widespread popularity, its efficacy in achieving clinically significant improvements and the mechanism of these improvements remain to be established. A randomized double-blind clinical trial of IMT would be required to help address the issue of clinically significant improvements. Since general exercise programs are at least as successful as IMT in improving patient performance,5,17-19 the efficacy and effectiveness of IMT and general exercise need to be compared. The application of objective techniques to evaluating respiratory muscle function would do much to elucidate the link between IMT, inspiratory muscle training, and exercise performance.

**Inspiratory Muscle Rest**

A strong argument can be made that the ventilatory failure of patients who develop acute severe asthma or fail to be weaned from a mechanical ventilator is the result of respiratory muscle fatigue.20 It is plausible and also unproved that hypercapnia in stable COPD may be caused by muscle fatigue of a chronic nature.21 The difficulty in testing such a hypothesis arises from the fact that fatigue is hard to demonstrate in the clinical setting, and indeed chronic fatigue as a cause of ventilatory failure is entirely hypothet-

Inspiratory muscle fatigue has been demonstrated in normal healthy subjects who breathe through external mechanical loads.22-24 In these experiments fatigue of the diaphragm, defined as the inability to generate a certain preset transdiaphragmatic pressure, has been shown to be associated with EMG changes (a shift in the power spectrum toward lower frequencies) and a reduction in contractile force to supramaximal phrenic nerve stimulation. Low frequencies of stimulation are reduced more than high and require a longer time for recovery.23,24 The mechanisms underlying these electrophysiologic events are unknown, making it difficult to predict the outcome of therapeutic interventions. One might anticipate that training of the inspiratory muscles would be effective in enhancing their performance, whether or not some of the muscle fibers were "fatigued." In the absence of fatigue, it is less clear that improvements in performance would result from rest therapy.

Even if we accept that inspiratory muscle fatigue may be present in patients with advanced COPD, the nature of the fatigue needs to be clarified. An old idea, but an attractive one from a teleologic point of view, is the notion of "central fatigue." Central fatigue means a failure of muscular contraction caused by a reduction in CNS output. An approach that is used to distinguish peripheral fatigue from central fatigue is to administer a shock or a series of shocks to the muscle when it is fatiguing in the operational sense. In pure peripheral fatigue, muscle recruitment should be maximal and force unchanged by superimposed shocks. If added shocks increase force, activation is not maximal and central fatigue is present. Bellemare and colleagues have shown that supramaximal stimulation of the phrenic nerves of trained subjects cannot elicit contractions of the voluntarily maximally contracted nonfatigued diaphragm.25 In contrast, shocks administered at the end of a fatiguing run do elicit an additional response, indicating that the diaphragm is no longer maximally activated by maximal voluntary effort under these conditions. The site of such central inhibition or failure of neurotransmission is not known. It is of interest, however, that motoneurons subjected to constant current stimulation do not maintain the initially high rate of impulse generation but "fatigue" at a rate related to the fatigability of the motor unit subserved by the motoneuron.26

The finding of changes in the EMG power spectrum, attributed to alterations of the velocity of conduction of action potentials in muscle, and low-frequency fatigue, a reflection of impaired excitation-contraction coupling, have been interpreted as evidence of "peripheral fatigue." Merton et al27 demonstrated that direct stimulation of the fatigued adductor pollicis resulted in a reduced force of contraction, whereas action potentials in the muscle evoked by stimulation of the motor cortex did not diminish, suggesting that the motor pathways tested were conducting normally. Whether these results hold true for the respiratory muscles remains to be tested. It is also not necessarily true that central inhibition is not taking place with voluntary contractions even if responses evoked by cortical stimulation do not suggest it. It is probable that both central and peripheral fatigue occur together and are presumably linked mechanistically. In the absence of conclusive scientific data
concerning the relative importance of central versus peripheral fatigue and the prevalence of fatigue of either kind in patients with respiratory failure, we will have to rely on empiric approaches to designing rehabilitative measures.

Respiratory muscles can be unloaded in patients with COPD by the application of cyclic negative pressures to the chest wall. Dyspnea and the oxygen cost of breathing are reduced by such a maneuver. The possible therapeutic value of so-called daily intermittent rest of the respiratory muscles in patients with COPD was signaled by an interesting report by Braun and Marino. Although in a previous description of the effects of intermittent ambulatory negative pressure ventilation on arterial blood gases and clinical well-being in patients with COPD, improvements were attributed largely to rest and improved ventilatory muscle function, no data were reported that could allow assessment of this hypothesis. Braun and Marino reported significant improvements in inspiratory muscle strength, blood gases, and vital capacity in 18 patients who received ventilation for 4-10 h/day for several months. Two very recent studies of "ventilatory muscle rest" (VMR) of shorter duration also purported to show significant improvements in patients with severe COPD and respiratory failure. In contrast, Zibrak et al., using a crossover design, failed to show any improvement in 20 patients with stable severe COPD. Furthermore, 11 of the patients were unable to tolerate ventilator treatment. All of these studies have limitations. In 2 of the studies showing benefit from VMR there were no controls, and in 1 of these studies no data were presented to permit the evaluation of the stability of the patients and whether or not they had suffered from a recent exacerbation. The study by Zibrak et al is perhaps better viewed as an effectiveness trial, in that compliance with treatment was limited (average use of VMR 4.1 h daily). In addition, no attempt was made to evaluate the degree of inspiratory muscle suppression achieved by VMR. Among the studies that report the efficacy of VMR, the total duration of therapy and the time per session varied substantially. As little as 8 h once weekly has been suggested to be beneficial. Furthermore, the degree of inspiratory muscle suppression was not always objectively assessed. It seems likely then that the failure of Zibrak to demonstrate efficacy relates to the choice of patients studied rather than the VMR.

In 1986, an NIH-sponsored randomized controlled clinical trial of VMR was initiated by PT. Macklem and colleagues at McGill University. The purpose of the trial was to evaluate the effectiveness of VMR in patients with severe COPD in alleviating dyspnea, improving exercise performance and quality of life. The trial was not designed to establish the efficacy of VMR but rather to see whether it could be applied effectively and in a general way to patients with severe COPD. In designing the study, we were concerned that sham VMR would not be feasible from the standpoint both of compliance and of patients remaining blind to the form of treatment. We investigated the problem in a pilot study of 32 patients who were randomized on a 2-to-1 basis to sham or active VMR. Surprisingly, sham VMR was as well tolerated as active VMR, and patients did not become unblinded to the form of VMR they were receiving. Therefore, the final design of the study was a two-arm randomized trial of active versus sham VMR. The pilot study also showed that nocturnal VMR was poorly tolerated, causing difficulty with sleep, so that we decided to test the effectiveness of VMR administered either during the day or night, as chosen by the subject.

The primary outcome variable for the study was exercise tolerance by the 6-minute walk test. The endurance time on a cycle ergometer at two-thirds of the peak power output was also evaluated, as was dyspnea (ATS questionnaire) and limitation by the oxygen cost diaphragm. A total of 1,231 subjects were interviewed. Approximately one-fourth met eligibility criteria (Table 1) and agreed to participate. The 348 recruited subjects participated in a 4-week stabilization period, during which it was established that appropriate bronchodilator medications were prescribed and being taken and that the lung function was stable. During stabilization, 164 subjects were excluded for various reasons. After 1 week of in-hospital training, during which time randomization took place, subjects were sent home with a negative pressure respirator, chest cage, and body wrap, which they were instructed to use for 8 h/day. Patients were stratified according to whether they used home oxygen or not. All baseline measures were obtained during hospitalization, including tests of the efficacy of the degree of suppression of the diaphragmatic EMG by VMR, recorded using surface electrodes.

Preliminary analysis of the trial has been completed. Table 2—Baseline Characteristics of Randomized Patients

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<tr>
<th>Measurement</th>
<th>Sham</th>
<th>Active</th>
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<tr>
<td>Age (yr)</td>
<td>65.2 (7.97)</td>
<td>63.6 (7.32)</td>
</tr>
<tr>
<td>% male</td>
<td>75%</td>
<td>70%</td>
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<tr>
<td>FEV1 (L)</td>
<td>0.75 (0.25)</td>
<td>0.78 (0.32)</td>
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<tr>
<td>% on home O2</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>6-min walk (m)</td>
<td>315.2 (103.3)</td>
<td>319.3 (111.15)</td>
</tr>
<tr>
<td>Time on cycle ergometer (min)</td>
<td>6.86 (4.37)</td>
<td>7.84 (6.56)</td>
</tr>
<tr>
<td>Visual analog scale (mm)</td>
<td>49.3 (13.94)</td>
<td>51.3 (15.38)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>6.7 (1.76)</td>
<td>6.5 (2.01)</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>71.3 (11.83)</td>
<td>70.9 (9.36)</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>44.4 (7.30)</td>
<td>43.8 (6.66)</td>
</tr>
<tr>
<td>Pr max (cm H2O)</td>
<td>44.4 (15.72)</td>
<td>41.7 (14.72)</td>
</tr>
<tr>
<td>Pr max (cm H2O)</td>
<td>82.0 (32.57)</td>
<td>84.4 (40.51)</td>
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Table 1—Eligibility Criteria for Clinical Trial of VMR

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<th>Entry criteria</th>
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<tr>
<td>Age 30-75 yrs</td>
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<tr>
<td>Clinical diagnosis of COPD</td>
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<tr>
<td>FEV&lt;30% predicted</td>
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<tr>
<td>FEV/FVC&lt;60%</td>
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<tr>
<td>FEV&lt;60% postsalbutamol</td>
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<tr>
<td>Dyspnea grade IV or V (ATS questionnaire)</td>
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<tr>
<td>Resting PaO2&gt;55 mm Hg (if PaO2 was less than 55 mm Hg, long-term O2 was prescribed prior to entry into study)</td>
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<th>Exclusion criteria</th>
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<tr>
<td>Morbid obesity</td>
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<tr>
<td>Asthma</td>
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<tr>
<td>Unstable angina</td>
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<tr>
<td>Recent myocardial infarction</td>
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<tr>
<td>Brittle diabetes</td>
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<tr>
<td>Recent exacerbation of COPD</td>
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<tr>
<td>Inability to exercise on a cycle ergometer</td>
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total of 184 patients were randomized. Baseline characteristics indicated that the active and sham groups were comparable at the outset (Table 2). The results of the trial did not show effectiveness of active VMR versus sham treatment. Neither measure of exercise tolerance showed improvement, nor did dyspnea, quality of life, arterial blood gases nor maximal inspiratory (Pi max) and expiratory pressures (Pe max). When subjects with the greatest severity of disease were examined (those on home O2, FEV1 <25% predicted, an ideal body weight <90% predicted), there was still no evidence of a treatment effect. When subjects whose average use of the ventilator was more than 26 h/week (N =61) were considered, there was still no evidence of a treatment effect.

VMR is therefore not a treatment form that can be recommended for general use in advanced COPD. The results raise the question of whether inspiratory muscle "fatigue" is present in advanced COPD and whether, if present, it is a form of fatigue that is affected by rest of the muscles. Hypercapnia in COPD is certainly not a serious obstacle to achieving substantial improvements in performance by exercise training. We cannot conclude from the results of our trial that certain patients with severe respiratory failure from COPD may not benefit from VMR, but we are unable to identify such patients currently. It is possible that benefits may be derived from nocturnal VMR, if tolerated, for reasons entirely unrelated to ventilatory muscle function. Before considering VMR as a therapy, we need to return to the study of the physiologic effects of this modality of ventilation using objective tests that permit more conclusive statements concerning inspiratory muscle function.

Nutritional Intervention in COPD

Malnutrition is a frequently encountered problem in patients with severe COPD. Although it is not an invariable accompaniment of respiratory failure, it is a marker of severe disease and has an adverse prognosis, independent of the usual measures of severity of disease. The reported prevalence of malnutrition varies according to the population surveyed and ranges from one-third to one-half of patients. Malnutrition has been shown to adversely affect respiratory function in subjects with and without lung disease. Maximum respiratory pressures have been reported to be lower in malnutrition, and diaphragmatic muscle mass at autopsy has been found to correlate with the muscularity of the subject, suggesting that the inspiratory muscles suffer the same degree of atrophy as skeletal nonrespiratory muscles. It is possible that inspiratory muscle failure may be more likely to occur in COPD patients who are malnourished than in those who are not.

Studies published to date have often addressed malnutrition in COPD without controlling for the effects of such confounding variables as FEV1, arterial Po2, etc. We have had the opportunity to examine the importance of malnutrition on exercise performance, dyspnea, and quality of life in a sample of 135 of the cohort of patients recruited for VMR. Thirty-three of the 135 subjects had a body weight <90% predicted body weight (IBW). We grouped subjects in 3 categories: <90%, 90-119%, >120% IBW. There was no difference in FEV1 (% predicted) among the 3 weight groups. %IBW was a weak predictor of both expiratory muscle strength (r2 =.16, p<.01) and inspiratory muscle strength (r2 =.05, p<.01). After correction for the association with FEV1, peak exercise performance on cycle ergometry (VO2 max, % predicted) was significantly associated with IBW (%). In contrast, performance on the 6-minute walk test was not associated with nutritional status. Similarly, the oxygen cost score, which measures the perceived degree of limitation of activity, was not related to nutritional status. The discrepancy between the relationship of VO2 max to nutritional status and the absence of any such relationship for other measures is consistent with the animal data that low oxidative fibers are more susceptible to atrophy. These fibers are more likely to be recruited during high-intensity exercise than during the low-intensity 6-minute walk test. Since slow oxidative fibers are better preserved, at least in rats and hamsters, it is a plausible hypothesis that low-intensity exercise may be spared from the adverse effects of malnutrition. It is also pertinent to ask ourselves whether we should use improvement in VO2 max as an indication of a successful clinical intervention if such changes are not also found at rest or during low-intensity exercise, which is after all more relevant to day-to-day functioning.

We are forced to conclude that weight loss is a marker of disease severity, but it may not contribute importantly to the symptomatology of the patient with COPD. Several small-scale intervention studies aimed at improving nutritional state have demonstrated the difficulty in accomplishing significant weight gain. The study of Effhimioiu et al suggests that, if weight gain can be effected, clinically significant improvements may result. Attention will need to be paid to the strategies to be used but also to the evaluation of the outcome of nutritional repletion.

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Home Care Rehabilitation and Perception of Dyspnea in Chronic Obstructive Pulmonary Disease (COPD) Patients

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Exercise training is reported to reduce dyspnea during exercise in COPD patients. We investigated the influence of a pulmonary rehabilitation program (PRP) including exercise reconditioning on the awareness of dyspnea (DY) and leg muscle fatigue (LMF) during exercise. Thirty patients, all with CAO and dyspnea on exertion were selected. After randomization, the patients were divided into a therapy group (TG) and a control group (CG). The TG followed a PRP, given by a home care team (general practitioner, nurse and physiotherapist). Before the start of PRP, these team members were instructed by a pulmonol-