may have been enhanced by the twice weekly visits of an investigator. In the absence of such supervision, one must rely on the patient’s own motivation to achieve adequate compliance in the home.

de Jong and coworkers do not address how to enhance compliance with an unsupervised exercise training program at home. Compliance may be sufficient if the patient is motivated by the benefit received from exercise, and if the exercise itself is interesting, or at least not unpleasant.

de Jong and colleagues make the important observation that their exercise training program improved CF patients’ abilities to perform activities of daily living. This may be an important motivation for patients with severe lung disease who may have substantial limitation in ability to perform activities of daily living. To this end, improvement in the ability to perform submaximal exercise may be more important than increasing the maximal oxygen consumption. The subjects in the study of de Jong et al increased their anaerobic threshold, suggesting that their endurance for exercise at levels which may be required for activities of daily living was increased.

The home exercise training study reported by de Jong and colleagues is an important step which helps to establish that it is possible to motivate CF patients to participate in a long-term exercise training program at home. Although many believe that encouraging exercise programs for chronic lung disease patients will be beneficial to their health, several questions remain unanswered. Does regular exercise improve the health or survival of chronic lung disease patients? Are the effects of exercise training equally beneficial to patients with mild vs severe lung disease? Is exercise ever harmful for patients with lung disease? Answers to these questions may help us determine the importance of encouraging exercise training for patients with chronic lung disease. If exercise is ultimately proven to be beneficial, then de Jong and his colleagues have shown us that these programs can be successfully instituted in the patient’s home.

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Life Expectancy in Severe COPD

Life expectancy in patients with severe COPD is strongly correlated with the severity of airflow obstruction. Some studies have also indicated an association between the degree of secondary pulmonary hypertension and survival. Long-term oxygen therapy (LTOT) ameliorates the pulmonary hypertension resulting from chronic hypoxemia and also improves survival, at least in patients with COPD. Some investigators have found that the fall in pulmonary artery pressure is predictive of improved survival. An analysis of the combined data from the NIH and MRC studies has led to the development of international prescribing criteria for the prescription of LTOT. Most countries which have adopted such criteria require an arterial oxygen tension below 55 mm Hg, breathing air in chronic stable state, and stipulate that oxygen should be administered for at least 15 h each day.

While LTOT is usually prescribed with the conviction that patients will survive longer due to an amelioration of pulmonary hypertension, our understanding of the pathophysiology and exact cause of death in patients with severe COPD is far from complete. What can be expected is a relentless deterioration in airway function with a decline in FEV₁, despite LTOT. Also, the histologic abnormalities which disrupt the pulmonary arterioles in the presence of chronic hypoxemia have been reported to continue right up to the time of death in patients who have LTOT. Other investigators have reported that LTOT reverses the pulmonary hemodynamic disturbances in COPD. Yet those studies which associate a fall in pulmonary artery pressure (Ppa) with improved survival have, without exception, demonstrated very modest reductions in Ppa (generally about 2 to 5 mm Hg). Perhaps such changes are not directly responsible for improved survival.

This issue of Chest includes an analysis by Dubois et al (see page 469) of survival in 270 patients with severe COPD who received LTOT according to the prescribing criteria of the Belgian Social Security regulations. The survival proportions for these patients were slightly worse than other reported groups (43 percent alive after 3 years), probably because they had more severe disease and patients without COPD were rigorously excluded. Complex statistical methods were used to seek associations between various physiologic parameters and survival. The strongest associations were with reduced transfer coefficient (TLCO/VA), severity of airflow obstruction, and poor response to oxygen administration in terms of the rise in PaO₂. Studies of this nature only expose associations between various parameters and do not allow us to draw any conclusions regarding the cause of death in severe COPD or the means of improved sur-
vival with LTOT. However, this report is interesting in that chronic hypercapnia appeared to be associated with better survival. Campbell was the first to suggest that permissive hypercapnia might be a physiologic adaptation which allows a greater CO₂ output for a given level of minute ventilation. In other words, for a given CO₂ output, the ventilatory requirement is less if the arterial PaCO₂ is allowed to rise and the work of breathing would be correspondingly reduced. A distinction is necessary between "permissive hypercapnia," as seen in the blue and bloated type of COPD patient, and "progressive hypercapnia" due to terminal respiratory failure. Permissive hypercapnia might, indeed, be a physiologic adaptation which leads to better life expectancy, whereas progressive hypercapnia can be expected in the final stages of severe COPD with or without LTOT.

We need to explore alternative explanations for the beneficial effect of LTOT and consider the precise reason for death in patients with severe COPD. Patients most commonly die of terminal respiratory failure due to overwhelming problems with ventilatory mechanics and gas exchange. Predictably, this clinical course will be accompanied by worsening hypoxemia and hypercapnia. Alternatively, some might die of dysrhythmias or myocardial infarction secondary to hypoxemia. Clinical experience suggests that patients do not die from the hemodynamic disturbances which arise in the pulmonary circulation. Why, then, is LTOT effective? One possible answer emerges when we re-examine the NIH and MRC data. Survival in the NIH group supposedly having continuous oxygen therapy was noticeably better than for the MRC group having oxygen for 15 h per day. This might not be remarkable but for the fact that these NIH patients were not fully compliant, and in practice, received oxygen for only about 18 h per day. The difference between these groups might lie not so much in the duration of oxygen therapy taken each day (a difference of only about 3 h), but more in the means of oxygen administration. The NIH patients were provided with apparatus for ambulatory oxygen therapy, whereas the MRC patients had fixed installations and were effectively confined to their homes. Part of the benefit of LTOT might therefore derive from patients' increased ability to physically exercise and offset the vicious cycle of disability which is almost inevitable in patients with chronic respiratory disease.

What can we conclude about life expectancy in patients with severe COPD, appropriate treatment measures, and the effects of LTOT? Certainly physicians are obliged to recognize the overriding importance of the airways obstruction and recommend vigorous bronchodilator therapy. Interestingly, the survival prospects of patients in the multicenter clinical trial of intermittent positive pressure breathing were equivalent to patients supposedly having continuous oxygen therapy. This would suggest that intensive bronchodilator therapy is equally as important as LTOT. The importance of maintaining physical activity has probably been underestimated, and LTOT might be beneficial, particularly in facilitating exercise. Finally, should we reconsider manipulations of respiratory drive in the management of COPD bearing in mind that permissive hypercapnia might be a physiologic adaptation contributing to better life expectancy? The traditional approach has been to stimulate respiratory drive with drugs such as methylxanthines. An alternative strategy worth exploring is the suppression of respiratory drive to allow a mild degree of hypercapnia and thus reduce ventilatory requirement. Oxygen is the only drug which can do this without fear of worsening hypoxemia. Perhaps this is another mechanism by which it improves survival in patients with COPD.

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Noninvasive Positive Pressure Ventilation in Neuromuscular Disease

Enough is Enough!

The efficacy of intermittent noninvasive ventilation in stabilizing respiratory failure and symptoms of hypoventilation in patients with slowly progressive neuromuscular diseases was first reported well over a decade ago. The earlier studies used mainly negative pressure ventilators, but because of greater convenience, portability, and avoidance of the sleep apnea induced in many patients by negative pressure ventilation, noninvasive positive pressure ventilation (NPPV) has become the mode of first choice in recent years. Within the past 6 years, numerous studies using NPPV have confirmed the earlier findings that intermittent noninvasive ventilation, mainly nocturnal, is associated with reversal of hypercapnia and symptoms in patients with chronic respiratory failure due to many neuromuscular diseases.

Despite the unanimously favorable results of the prior studies, no controlled, prospective trials have been done to confirm the efficacy of NPPV. Such studies were not done mainly because withholding from control subjects what was almost certainly effective treatment to prove survival benefit would have been ethically unjustifiable. In the present issue of Chest (see page 445), Vianello and colleagues have avoided this ethical problem by comparing the clinical course of five patients with Duchenne muscular dystrophy (DMD) who accepted nasal NPPV with that of five patients who refused. Although the number of patients enrolled was small, the results seem unequivocal after two years of follow-up, all nasally ventilated patients were alive, whereas four of the five “control subjects” had died.

Should we now accept that nasal NPPV is highly effective at improving survival in this patient population? The doubters will point out that in addition to the small number of patients in this trial, it was not randomized, and although the baseline differences between the groups were not statistically significant, there was a trend toward greater age, lower Vt, and higher PaCO2 in the “control” group, perhaps predisposing to the higher mortality. Despite these limitations, however, the evidence in the present study combined with that of the numerous previous studies renders virtually unequivocal the conclusion that NPPV is highly efficacious in improving gas exchange abnormalities, symptoms, and survival in patients with DMD and with other slowly progressive neuromuscular diseases as well.

Despite the convincing nature of the survival data, the contention that NPPV stabilizes respiratory muscle function in patients with DMD must be scrutinized. The study followed patients for only 2 years, and some initial improvement in pulmonary function might have been anticipated if NPPV alleviated hypoxemia or hypercapnia. Such an improvement could have masked the loss of pulmonary function related to the inexorable progression of the underlying disease. Whether or not NPPV alters this progression in any way other than by stabilizing gas exchange is unclear, but previous studies demonstrate that even with effective noninvasive ventilation, pulmonary function eventually deteriorates, with the patient using the ventilator for more and more time each day. Tracheostomy might eventually be advised, although certain investigators have reported success in managing patients with NPPV who have virtually no capacity for spontaneous breathing.

At the present time, NPPV, initially nocturnal, should be considered the treatment of first choice for symptomatic patients with chronic respiratory failure due to slowly progressive neuromuscular diseases such as DMD, other muscular dystrophies, postpolio syndrome, or occasional patients with multiple sclerosis or amyotrophic lateral sclerosis who have intact upper airway function. Exceptions might include those thought to have a major component of central hypoventilation who could try progesterone initially, and those with significant obstructive sleep apnea who could try nasal CPAP; but patients not responding successfully should receive NPPV. Other noninvasive ventilators should now be considered second choices, to be offered to patients who fail to tolerate NPPV. The evidence to support this approach has become so strong that the focus of investigation should now shift from questions of NPPV efficacy to questions of how it works, and how its implementation can be optimized.

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