

Domiciliary ventilation in chronic obstructive lung disease

Improvement in the understanding of the basic mechanisms of disease should lead to the development of new and better treatments. Sometimes the initial rationale for such treatment changes, and this appears to be the case with the relatively new technique of intermittent positive pressure ventilation, technical aspects of which have recently been reviewed.¹

Respiratory muscle fatigue

A major stimulus to the development of domiciliary ventilation was the report in 1977 that the diaphragm, like other skeletal muscle, could be made to fatigue—that is, fail to sustain the desired or expected force.² Since then a host of publications (reviewed in refs 3–5) have defined the biochemical and physiological determinants of fatigue. Several tests have been developed to measure impending or established failure of respiratory muscle force generation.^{6–10} These assess either the altered activation or relaxation of the respiratory muscles during voluntary contractions^{6–8} or the ability of the muscle to respond to external electrical stimulation, usually via the phrenic nerve.^{9,10} The power spectrum of the electromyogram of respiratory muscle changes as fatigue develops, a relatively greater contribution being made from the lower frequencies. This fall in the ratio of power in the high to the low frequency bands (H:L ratio) was one of the first objective measure of respiratory muscle fatigue.⁶ Others have used the slowing of muscle relaxation that occurs as fatigue develops⁷ or the failure to develop high initial driving pressures during loading.⁸ Studies of the force developed after phrenic nerve stimulation by trains of impulses of differing frequency⁹ or during relaxation or voluntary activation of muscle¹⁰ have been advocated as more objective tests of the force generating capacity of these muscles. Bellemare and Grassino developed the concept of the tension-time index of the diaphragm (TTdi) as an indirect measure of respiratory muscle energy consumption.¹¹ They found that when the duration of inspiration (Ti) expressed as a percentage of the total respiratory duty cycle (Ti/Ttot) is multiplied by the pressure developed (Pdi) as a percentage of the maximum static pressure (Pdimax) a constant resulted ($TTdi = Ti/Ttot \times Pdi/Pdimax$). These workers found empirically that when this constant exceeded 0.15 respiratory muscle fatigue, as assessed by electromyographic criteria and endurance time, would always develop. They showed that the force reserve of the diaphragm is smaller in patients with severe chronic obstructive lung disease and hence the risk of developing fatigue is greater.¹²

Surprisingly, there is a paucity of data confirming the presence of diaphragmatic fatigue in acute clinical conditions but serial observations of the H:L ratio showed that this occurred in six of 12 patients during trials of weaning from assisted ventilation.¹³ Patients with electromyographic fatigue had a rapid, shallow breathing pattern and developed paradoxical rib cage movements during inspiration. The finding that similar breathing patterns occur during unfatiguing loading¹⁴ has cast doubt on the general usefulness of these signs. Early reports suggested that respiratory muscle fatigue was an important mechanism of dyspnoea in such patients¹⁵ but subsequent investigation makes this unlikely.¹⁶

Several different forms of respiratory muscle fatigue have been described, depending on which part of the activation pathway of muscle contraction from the cerebral cortex to intracellular calcium release has been disturbed.¹⁷ Failure

to generate force at high frequency (high frequency fatigue) is short lived and probably not relevant to normal physiology as the stimulation frequencies exceed those seen in vivo. Low frequency fatigue is more sustained and may occur at levels that might be seen in life. Central fatigue appears to be a protective mechanism whereby the muscle reduces the central neuronal firing frequency by some poorly understood mechanism but still retains the capacity to respond to direct stimulation. Each of these must be distinguished from failure to activate the muscle for behavioural reasons, which may prove to be the most important mechanism of all. Tests such as the H:L ratio reflect short lived changes in membrane potential due to high frequency stimulation rather than a longer term reduction in force generation due to loss of contractile function, as occurs after low frequency stimulation.¹⁸ The possibility of persistent functional loss led to speculation that chronic hypoventilation was a result of this low frequency fatigue.¹⁹ As muscle rest allows low frequency fatigue to recover, a feature so characteristic that it is now included in one of the recently proposed definitions of fatigue,⁵ it followed that respiratory muscle rest in the form of assisted ventilation would relieve chronic fatigue and produce a sustained correction of hypercapnia. Because hypercapnia itself further impairs respiratory muscle function²⁰ its correction might break a vicious circle perpetuating the fatiguing process.

Intermittent negative pressure ventilation in chronic obstructive lung disease

Before this theoretical rationale was developed some clinicians had experience of domiciliary ventilation in patients with chronic respiratory failure who were capable of spontaneous ventilation by day. A few patients with kyphoscoliosis, both young²¹ and old,²² or a previous thoracoplasty²³ could be kept at home with a more normal daytime arterial carbon dioxide tension (Paco₂) produced by regular night time negative pressure ventilation. When this treatment was given to hypercapnic patients with chronic obstructive lung disease in an open, uncontrolled trial, dramatic improvements in daytime Paco₂ and, more importantly, in inspiratory muscle pressures occurred.²⁴ The latter finding suggested that treatment was reversing inspiratory muscle fatigue and led several groups to test this form of treatment^{25–30} (table). The duration and frequency, the period of follow up, and the measures of outcome varied between the trials but a consistent pattern of improvement was seen in patients with substantial hypercapnia while little if any change occurred in relatively normocapnic patients with airflow limitation.

The implications of successful treatment for such a common problem led the National Heart, Lung, and Blood Institute in the United States to set up a controlled trial of respiratory muscle rest by cuirass respirator, the design of which has recently been reported.³¹ The patients studied had stable chronic obstructive lung disease, a forced expiratory volume in one second below 50% predicted, and an FEV₁/forced vital capacity (FVC) ratio below 60% as well as grade 4 breathlessness (on the basis of the American Thoracic Society criteria). Most were normocapnic and received ventilation by day, though precise details of the duration of treatment are not yet available. Care was taken to ensure that ventilatory synchrony was obtained and intrinsic respiratory muscle activity was suppressed to ensure that the respiratory muscles were rested.³² Although the results have not been formally published, preliminary

Published results of intermittent negative pressure ventilation in chronic obstructive lung disease

Reference	Number*		Treatment allocation	Treatment	Follow up	FEV ₁ (l)†	Paco ₂ (kPa)		MIP (cm H ₂ O)†		Comment
	Starting study	Completing study					Initial	Final	Initial	Final	
Braun and Marino ²⁴	18	18	Open	4–10 h daily	5 months	—	7.2	6.0	36%	58%	Hospitalisation reduced
Cropp and di Marco ²⁵	15 (8)	15 (8)	Randomised	3–6 h daily	3 days	0.8	8.0	6.9	67	77	Sustainable ventilation increased
Gutierrez et al ²⁶	5	5	Open	8 h once weekly	4 months	27%	7.8	6.8	45	62	Slower, deeper breathing pattern
Zibrak et al ²⁷	20	9	Crossover	2–6 h daily	6 months active	0.55	6.3	6.7	30	30	High dropout rate
Celli et al ²⁸	16 (9)	14 (8)	Randomised	3–11 h daily	3 weeks	0.60	6.0	5.6	—	—	Training improved exercise tolerance in both groups
Ambrosina et al ²⁹	18 (10)	18 (10)	Randomised	6 h daily	5 days	0.77	7.5	6.8	34	42	12 minute walk improved
Scano et al ³⁰	11 (6)	11 (6)	Randomised	4 h daily	7 days	28%	8.0	6.8	41	45	Slower, deeper breathing pattern

*Numbers actively treated in parentheses.
†Except where “%,” meaning “% predicted,” appears.

presentations in Europe and North America by the senior investigators indicate that no difference in any functional or mortality related variable was seen among the 184 patients randomised for treatment with active or sham ventilation. Even more recently, evidence has been presented showing that the diaphragm of patients with normocapnic chronic obstructive lung disease is capable of developing pressures similar to those of normal individuals, with no evidence of chronic fatigue.³³

Intermittent positive pressure ventilation in chronic obstructive lung disease

A major difference between the studies at the National Heart, Lung, and Blood Institute on patients with chronic obstructive lung disease and those on patients with chest wall disorders is that the latter patients received overnight ventilation, which was not tolerated by the patients with chronic obstructive lung disease. Negative pressure ventilation by tank respirator, Cuirass shell, or pneumosuit is cumbersome and often uncomfortable because of the fixed body position. It may also induce upper airway obstruction during sleep and hence a sleep apnoea syndrome.³⁴ A major advance came when Ellis and colleagues showed that nasal intermittent positive pressure ventilation was possible in patients with neuromuscular disease.³⁵ The mechanism of sleep related oxygen desaturation in neuromuscular disease is different from that in chronic obstructive lung disease.³⁶ Nevertheless, a study in four patients with chronic obstructive lung disease and six with restrictive disorders confirmed that increases in oxygen tension and falls in carbon dioxide tension could be produced with nasal intermittent positive pressure ventilation³⁷ and patients almost invariably preferred it to the negative pressure respirator when treatment was required for less than eight hours a day. If respiratory muscle rest is achieved in this way, can it influence blood gas tensions and general wellbeing favourably in patients with chronic obstructive lung disease?

This problem is addressed in a study reported in this issue of *Thorax*,³⁸ where 12 patients with severe chronic obstructive lung disease (mean FEV₁ 0.6 l, mean Paco₂ 7.7 (SD 0.9) kPa) and cor pulmonale were treated in an open study of nasal intermittent positive pressure ventilation. After six months' treatment eight patients were still using their ventilator and at one year seven patients. Small but significant changes in daytime blood gas tensions occurred in those using nocturnal ventilation, which raised nocturnal oxygen saturation and increased the total time slept above the baseline level. Self reported quality of life scores were unchanged but no data on exercise perfor-

mance are presented here. These authors did not find a relation between changes in inspiratory muscle strength and Paco₂ in a previous report based on this group of patients.³⁹ Some mechanical improvements were seen with a fall in residual volume and increased ventilatory response to hypercapnia after nasal ventilation. Unfortunately, in the paper presented in this issue³⁸ there is neither a placebo limb nor a control group and comparative data about sleep quality are not available for the patients who dropped out of the trial. In addition, two of the patients followed up were apparently not stable initially, which raises some concern about the likely size of the therapeutic benefit. This technique is clearly feasible in the long term but is it better than current treatment with domiciliary oxygen?

The future: problems and prospects

It is much easier to emphasise the limitations of data such as these than conduct this type of taxing clinical investigation. This topic is of increasing importance in North America and Europe, 31 papers about it being presented at the last meeting of the American Thoracic Society.⁴⁰ The financial implications of the widespread introduction of this treatment are considerable. Domiciliary ventilators currently cost about £3500 and substantial support is needed from doctors, physiotherapists, and nurses. What must future trials do to convince the sceptics that this is money well spent?

Further trials of negative pressure ventilation are unlikely, given the lack of success in the Montreal study and the present report that long term nasal intermittent positive pressure ventilation is feasible in patients with chronic obstructive lung disease. Future trials must be large enough to escape the potential for type II errors, which have affected all currently published studies. They should offer an “intention to treat” analysis to include the dropouts as well as the survivors and should contain a control group randomly allocated to sham treatment or possibly long term oxygen therapy. Clear outcome measures, both functional and psychological, must be chosen and applied in a way that takes account of the extent to which they are known to be affected by practice. On present evidence hypercapnic patients benefit most but many of these would normally receive domiciliary oxygen. Assisted ventilation may, however, permit better oxygenation than would otherwise occur for a given level of respiratory acidosis and here may lie its greatest promise. Studies of sleep quality during oxygen therapy and during nasal intermittent positive pressure ventilation must be undertaken as improved oxygenation alone may improve sleep.⁴¹ Finally, further studies are urgently needed to determine which

ventilator system is most effective and whether there are real differences between pressure and volume cycled respirators.

Many physicians prefer drugs to devices and are more likely to accept a treatment based on accepted theory. At present the theoretical basis for nocturnal ventilation appears uncertain but the practical evidence in its favour, though imperfect and fragmentary, is growing. The history of domiciliary oxygen treatment holds some hope for the enthusiastic supporter of nocturnal ventilation. Small studies with encouraging but inconclusive results^{42 43} led to definitive investigations^{44 45} that confirmed that there was an important benefit and in the process showed that resolution of pulmonary hypertension, the original theoretical reason for using domiciliary oxygen, did not explain all of the treatment success. Twenty years after these pioneering observations we again face a dilemma about a promising new treatment for chronic obstructive lung disease that only carefully conducted large scale prospective trials can resolve. These should be established soon.

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