REVIEW

New strategies to improve exercise tolerance in chronic obstructive pulmonary disease

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New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. N. Ambrosino, S. Strambi. ©ERS Journals Ltd 2004.
ABSTRACT: Breathlessness is the most common symptom limiting exercise in patients with chronic obstructive pulmonary disease (COPD). Exercise training can improve both exercise tolerance and health status in these patients, intensity being of key importance. Nevertheless, in these patients extreme breathlessness and/or peripheral muscle fatigue may prevent patients from higher levels of intensity. In this review article the literature concerning the different ways to optimise exercise tolerance in patients with COPD, with the objective of enhancing the tolerance to higher exercise training intensity, is summarised.

Continuous positive airway pressure and different modalities of noninvasive positive pressure ventilation (NPPV) may reduce breathlessness and increase exercise tolerance in these patients. Respiratory muscle unloading and reduction in intrinsic positive end-expiratory pressure have been considered among mechanisms underlying these effects. Nevertheless, the role of NPPV in pulmonary rehabilitation, if any, is still controversial. The addition of nocturnal domiciliary NPPV during a daily exercise programme in patients with severe COPD resulted in an improvement in exercise tolerance and quality of life.

In patients with severe COPD application of electrical stimulation combined with active limb mobilisation significantly improved muscle strength, and interval training has been shown capable of inducing physiological training effects.

Oxygen supplementation in patients who do not desaturate during exercise seems to be the most promising treatment, since it allows for higher exercise intensities and, therefore, superior training efficacy.

In conclusion, further studies are needed to define the appropriate patients in order to generalise such interventions. The modalities discussed should be used as adjuncts to a well designed comprehensive respiratory rehabilitation programme.
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Only long-term oxygen therapy (LTOT) and smoking cessation improve survival in patients with chronic obstructive pulmonary disease (COPD) [1, 2]. COPD is a heterogeneous disorder characterised by dysfunction of the small and large airways, as well as by destruction of the lung parenchyma and vasculature, in highly variable combinations [3]. Breathlessness and exercise intolerance are the most common symptoms in COPD and progress relentlessly as the disease advances. In these patients, although the primary pathological changes are confined to the lungs, the consequent physical deconditioning and emotional responses contribute a large extent to morbidity. Increased breathlessness leads to inactivity and consequent peripheral muscle deconditioning, resulting in a vicious cycle leading to further inactivity, social isolation, fear of dyspnoea and depression. Patients with severe COPD become less mobile and reduce their activities of daily living (ADL). In a survey of patients with severe COPD treated with LTOT, 50% (Medical Research Council dyspnoea grade 5) did not leave the house and 78% were breathless walking around at home and performing ADL [4]. Multidisciplinary pulmonary rehabilitation may offer a useful tool [5]. In fact it has been shown that the utilisation of healthcare services by COPD patients is related more to respiratory and peripheral muscle force than to airway obstruction [6]. Moreover, in patients hospitalised with an acute exacerbation of severe COPD, 1-yr survival was reported to be independently related to nutritional status, as assessed by body mass index, and prior functional status [7]. Multidisciplinary rehabilitation can positively influence peripheral and respiratory muscle function, nutrition and ADL [8–11].

Mechanism of exercise dyspnoea

Pathophysiological factors known to contribute to exertional dyspnoea in COPD patients include increased intrinsic mechanical loading of inspiratory muscles, *i.e.* the intrinsic positive end-expiratory pressure (PEEPi), (the inspiratory threshold load (ITL)) [12], increased mechanical restriction of the thorax, inspiratory muscle weakness, increased ventilatory demand relative to capacity, gas exchanges abnormalities, dynamic airway compression, cardiovascular factors, and any combination of the above [13]. Besides lung function, peripheral muscle force is also an important determinant of exercise capacity in COPD. Peripheral muscle wasting is a

common finding in advanced COPD, as in several other chronic diseases [14]. Recent advances in clinical research have confirmed the negative impact of muscle wasting on patients′ survival [15], and, at the same time, improved understanding how muscle mass is maintained [16, 17]. The consequences of peripheral muscle wasting on therapeutic approaches should be taken into account. Gain in muscle mass and strength has been associated with better exercise tolerance and survival [15], therefore, improving peripheral muscle function could be a reasonable therapeutic target in patients with COPD. Pharmacological approach to this problem (*e.g.* anabolic steroid [18] and growth hormone [19] supplementation) is still questioned. Most probably, exercise training is the best available therapeutic modality to preserve muscle mass, since physical activity can decrease proteasome activity [20] and muscle redox potential in COPD [21].

Exercise training

Patients with COPD can achieve a physiological training effect from well-designed programmes of exercise training as a part of comprehensive pulmonary rehabilitation programmes. Patients with mild COPD respond to a programme of high intensity training with reduced levels of blood lactate and pulmonary ventilation at a given heavy work rate [22]. Substantial improvements in exercise tolerance can be obtained as a result of programmes of exercise training even in those patients with severe obstruction who are unable to elevate blood lactate levels. The improvements of exercise tolerance have been found to be accompanied by physiological changes, such as improved muscle function (including more rapid oxygen uptake kinetics following exercise onset) [23] and altered breathing pattern (higher tidal volume (VT) and lower breathing frequency that lead to a reduced dead space to VT ratio and thus to a lower ventilatory requirement for exercise [24]). Intensive training increases the levels of aerobic enzymes and the capillary density of leg muscle of patients with severe COPD as assessed by morphological and biochemical analysis of muscle biopsy specimens of thigh muscle [25, 26].

Aim of review

Given the demonstrated value of exercise training [27, 28], recent research has focused on methods to enhance the effectiveness of exercise training and, in addition, to define new approaches to improving muscle function. The rationale for such approaches is based on the above mechanisms of reduced exercise tolerance of COPD, namely respiratory muscle overburden and reduced peripheral muscle function. In this review article the literature concerning the different ways to optimise exercise tolerance in patients with COPD is summarised with the objective of enhancing the tolerance to higher exercise training intensity. Reviewing literature from 1980–2004 (PubMed) shows 986 articles under the terms COPD and rehabilitation. For the purpose of this review articles have been reviewed according the following terms: COPD and exercise and: 1) mechanical ventilation: 61 studies, including one methanalisis; 2) electrical stimulation: five studies; 3) interval training: 16 articles including two methanalisis; 4) oxygen: 101 studies; and 5) biofeedback: four studies.

Noninvasive ventilation and exercise

Exercise training as a part of multidisciplinary pulmonary rehabilitation can improve both exercise tolerance and health-related quality of life (HRQL) in COPD patients [27, 28].

Physiological changes contribute to these improvements: reduction of lactic acidosis, minute ventilation and heart rate for a given work rate, and enhanced activity of mitochondrial enzymes and capillary density in the trained muscles. Intensity of exercise training is of key importance. High-intensity training improved both maximal and submaximal exercise tests and induced both cardio-respiratory and peripheral muscle adaptations [22, 29, 30]. Nevertheless, in these patients extreme breathlessness and/or peripheral muscle fatigue may prevent patients from higher levels of intensity. As a consequence of flow limitation, to cope with the increased ventilatory demands of exercise, these patients show a breathing pattern that ultimately places greater demands on their inspiratory muscles. Indeed, in these patients a pattern of low VT and high frequency breathing is unlikely to be advantageous but is the only pattern available in the presence of expiratory flow limitation and dynamic hyperinflation. Increased inspiratory muscle work may contribute to dyspnoea and exercise limitation in such patients even before their ventilatory ceiling is attained.

How does NPPV work? In recent years there has been an increasing interest in the use of noninvasive positive pressure ventilation (NPPV) to increase exercise capacity of these patients. Reducing exercise dyspnoea, by unloading respiratory muscles by assisted ventilation, might allow for higher levels of exercise intensity. NPPV has been used in physiological studies in normals. By unloading respiratory muscles by means of proportional assist ventilation (PAV), a recent modality of mechanical ventilation [31], it has been shown in healthy trained cyclists that work of breathing (WOB) needed to sustain heavy-intensity exercise was correlated to a reduction in leg blood flow and had a significant influence on exercise performance [32, 33]. In other words there would be a competition for blood flow between respiratory and limb muscles. In another study PAV prevented exercise-induced diaphragmatic fatigue as determined by bilateral phrenic nerve stimulation at all frequencies and times post-exercise [34]. To the extent that intrinsic mechanical loading and functional inspiratory muscle weakness in COPD contribute to dyspnoea, assisted ventilation should provide a symptomatic benefit by unloading and assisting such overburdened ventilatory muscles. Several studies have examined the acute effects of different modalities of ventilatory assistance on dyspnoea and exercise tolerance in advanced COPD [35].

Continuous positive airway pressure. Theoretically, continuous positive airway pressure (CPAP) should reduce the ITL on the inspiratory muscles of hyperinflated COPD patients and enhance neuromuscular coupling, thus improving dyspnoea and exercise tolerance [36]. In a study by O′DONNELL *et al.* [37] in COPD patients (mean forced expiratory volume in one second (FEV1) 35% predicted) CPAP of 4–5 cmH$_2$O resulted in a significant increase in exercise endurance time. In another study these authors administered CPAP, 4–5 cmH$_2$O during steady-state submaximal exercise in COPD patients (mean FEV1 40% pred) and in healthy subjects [38]. CPAP, when administered to COPD patients, resulted in a highly significant reduction in the sense of breathing effort. In contrast, CPAP significantly increased the sense of breathing effort in the normal group. In a study of COPD patients (FEV1 25% pred) CPAP reduced inspiratory muscle effort, as indicated by the transdiaphragmatic and oesophageal pressure-time integrals [39].

The commonly accepted explanation of the effects of CPAP is that it counterbalances PEEPi, *i.e.* the ITL [13]. From the

above studies it can be also argued that for maximal benefit CPAP should be titrated on an individual basis to optimise comfort at pressure levels just below the ITL. Nevertheless, this should theoretically imply measurement of PEEPi, which is rather difficult to perform on a routine basis. CPAP was also shown to reduce the WOB and increase exercise tolerance in patients with cystic fibrosis. These beneficial effects were related to disease severity [40].

Pressure support ventilation. Inspiratory pressure support (IPS) is a form of mechanical ventilation that can effectively assist ventilation when applied noninvasively to patients in acute and chronic respiratory failure. Pressure support is a pressure-targeted mode in which each breath is patient triggered and supported [41]. It provides breath-by-breath ventilatory support by means of a positive pressure wave synchronised with the inspiratory effort of the patient. During inspiration, the airway pressure is raised to a preset level: the pressure support level. This level is maintained until the machine determines the end of a patient's respiratory effort or detects a patient's demand for expiration. The expiratory phase is free of assistance and a level of external PEEP, lower than the inspiratory plateau pressure can be applied [41].

The excessive load placed on inspiratory muscles when patients with COPD exercise could lead to fatigue and contribute to exercise limitation. Slowing of maximal relaxation rate (MRR) of skeletal muscle is an early index of the fatiguing process. KYROUSSIS *et al.* [42] found in COPD patients (mean $FEV1$ 28% pred) walking to exhaustion a post-exercise fall in oesophageal MRR, indicating that the inspiratory muscles of these patients were sufficiently heavily loaded to initiate the fatiguing process. The same authors gave a physiological confirmation of this hypothesis through an application of NPPV to unload inspiratory muscles during exercise in COPD patients [43]. They compared oesophageal MRR after equidistant treadmill walking. After a free walk there was a mean 41% slowing of oesophageal MRR. After noninvasive IPS assisted walks, the slowing of oesophageal MRR was significantly less than after the free walk.

KEILTY *et al.* [44] studied COPD patients with disabling breathlessness (mean $FEV1$ 0.73 L). Studies were performed with mask IPS (mean airway pressure 12–15 cmH_2O), CPAP 6 cmH_2O, and with oxygen (2 $L \cdot min^{-1}$ *via* the mask) in random order on three separate days. Each of these walks was compared with a control walk using a sham circuit (breathing air *via* a mask at 2 $L \cdot min^{-1}$ from an unlabelled cylinder), and with a baseline walk in which patients walked freely on the treadmill. No patients stopped due to leg fatigue, all stopping only when their sensation of breathlessness had reached level 5 on the Borg scale [45]. NPPV improved median walking distance by 62% compared with the control walk (sham circuit). There was no change in walking distance with either CPAP or oxygen at 2 $L \cdot min^{-1}$. There was no difference between the control and the baseline walks. In a study by MALTAIS *et al.* [46] severe COPD patients (mean $FEV1$ 0.75 L) performed constant workload bicycle exercise during control conditions and with the application of IPS (∼10 cmH_2O). IPS increased minute ventilation as a result of changes in both VT and respiratory rate. This occurred despite marked reductions in inspiratory effort, as indicated by the oesophageal and transdiaphragmatic pressure-time integrals. Breathlessness improved significantly with the addition of IPS and worsened to a similar degree when it was removed. In another study during exhaustive treadmill walking in patients with severe COPD, the oesophageal and transdiaphragmatic pressure/time products rose early in the walk and then remained at that level until the patients

stopped because of intolerable dyspnoea [47]. When patients walked the same distance assisted by IPS, a substantial reduction was observed in the inspiratory and expiratory pressure/time products throughout the walk. When patients walked with NPPV for as long as they could, the pressure/time products observed at exercise cessation were lower than those observed during exercise cessation after free walking. It was concluded that, in severe COPD, inspiratory muscle pressure generation did not increase to meet the demands imposed by exhaustive exercise.

Plasma lactate levels were measured in patients with severe COPD who performed two treadmill walks at an identical constant work rate to a condition of severe dyspnoea; the second walk was supported by IPS [48]. Lactate levels significantly increased during both walks to similar levels respectively, but the duration of the IPS-assisted walk was significantly greater than the free walk (13.6 *versus* 5.5 min). Therefore, it was argued that patients with severe COPD can sustain exercise-induced lactataemia for longer if assisted with IPS. Another more recent study has shown that in contrast to 5 cmH_2O, the application of IPS of 10 cmH_2O during exercise resulted in a statistically significant improvement in exercise endurance in patients with COPD, compared with exercise without IPS [49]. However, on an individual basis, large differences in responses were found.

Proportional assisted ventilation. Proportional assisted ventilation is a mode of partial ventilatory assistance endowed with characteristics of proportionality and adaptability to the intensity and timing of spontaneous ventilatory pattern by providing inspiratory flow and pressure in proportion to the patient's effort. The ventilator delivers pressure according to the motion equation, generating pressure in proportion to a patient's spontaneous effort. A portion of the total mechanical workload, *i.e.* elastance and resistance, is taken over according to a level of assistance, which has been decided by the caregiver and can specifically unload the resistive burden (flow assist) and the elastic burden (volume assist) [33, 50–52]. DOLMAGE and GOLDSTEIN [53] determined whether PAV applied during constant power submaximal exercise could enable severe, stable COPD patients (mean $FEV1$ 29% pred) to increase their exercise tolerance. Patients completed five sessions of cycling at 60–70% of their maximum power. The sessions differed only in the type of inspiratory assist: 1) baseline; 2) PAV; 3) CPAP (5 ± 2 cmH_2O); (4) PAV and CPAP; and 5) sham. Subjects reached the same level of dyspnoea (by Borg scale) during all sessions but only PAV and CPAP significantly increased exercise tolerance (12.9 min) *versus* the sham session (6.60 min). Mean exercise time during the PAV and CPAP sessions was 7.10 and 8.26 min, respectively.

BIANCHI *et al.* [54] investigated the impact of PAV, CPAP and IPS on exercise tolerance and breathlessness in severe stable chronically hypercapnic COPD patients. On two consecutive days, patients underwent four endurance tests on a cycle ergometer at 80% of their maximal workrate, receiving, *via* a nasal mask in random order, either: 1) sham ventilation (CPAP 1 cmH_2O); 2) CPAP 6 cm H_2O; 3) IPS 12–16 cmH_2O and PEEP 1 cmH_2O; or 4) PAV and PEEP 1 cmH_2O. Oxygen supply was standardised to maintain an arterial oxygen saturation of 92–93%. In comparison with sham ventilation, PAV, PSV and CPAP were able to increase the endurance time (from 7.2 to 12, 10 and 9.6 min, respectively) and to reduce dyspnoea and oxygen flow to the nasal mask. However, the greatest improvement was observed with PAV. Other authors have confirmed the utility of PAV to improve exercise tolerance in COPD patients [55].

Controlled mechanical ventilation. Assist-control ventilation is a combination mode of ventilation in which the ventilator delivers a positive pressure breath at a preset $V\text{T}$ in response to the patient's inspiratory effort. The ventilator will also deliver breaths at a preset rate if no patient effort occurs within the preselected time period [56]. Assist-control ventilation was delivered by means of a volume-cycled home ventilator and nasal masks during exercise in patients with pulmonary tuberculosis sequelae [57]. This modality of NPPV resulted in a significant improvement in breathlessness, and increase in exercise endurance in these patients. Nevertheless, this paper is still the only one reporting application of assist-control ventilation during exercise.

NPPV and pulmonary rehabilitation

The message of these physiological studies could be summarised as follows: acute NPPV, either CPAP, IPS or PAV, during exercise reduces dyspnoea and WOB and enhances exercise tolerance in COPD patients. A systematic review by VAN'T HUL *et al.* [58] identified 15 physiological studies dealing with use of NPPV during exercise. Seven of these studies met the inclusion criteria, including a total of 65 patients with COPD. The methodological quality of the included studies varied from 31–54% of the maximum score of 13 points. Statistically significant summary effect sizes were found in the analysis of exertional dyspnoea as well as in the analysis of exercise endurance, indicating improvements in these outcomes in favour of NPPV. Nevertheless, the role of NPPV in pulmonary rehabilitation, if any, is still to be defined. In fact, the recent development of new therapeutic approaches like lung transplantation and lung volume reduction surgery make patients with severe COPD, even with chronic respiratory failure, candidates to rehabilitation programmes [59, 60].

BIANCHI *et al.* [61] evaluated the effects of the addition of assisted ventilation during exercise training on the outcome of a structured pulmonary rehabilitation programme in COPD patients. Patients with stable COPD (mean FEV1 44% pred), without chronic ventilatory failure, undergoing a 6-week multidisciplinary outpatient pulmonary rehabilitation programme including exercise training, were randomised to training during either mask PAV or spontaneous breathing. Five of 18 patients (28%) in the PAV group but no patient in the control group dropped out due to lack of compliance with the equipment. Both groups showed significant post training improvements in exercise tolerance (peak work rate difference: 20 and 14 watts in PAV and control group, respectively), dyspnoea and leg fatigue, but not in HRQL, without any significant difference between groups. HAWKINS *et al.* [62] evaluated the effects of providing ventilatory assistance to patients with more severe COPD (mean FEV1 27% pred) during a 6-week supervised high intensity outpatient cycle exercise programme. Patients were randomised either to exercise with ventilatory assistance using PAV or to exercise unaided. Before and after training, patients performed a maximal symptom limited incremental cycle test to determine peak work rate followed by a constant work rate test at 70% of peak work rate achieved in the baseline incremental test. At 6 weeks mean training intensity and peak work rate were 15.2% and 18.4% higher in the group that used PAV. Iso-workload lactataemia after training was reduced by 30% in the assisted group and by 11% in the unassisted group. A significant inverse relationship was found between reduction in iso-workload lactataemia after training during the constant work rate test and peak work rate achieved during the last

week of training. The authors suggest that the reduction in plasma lactate concentration for a given workload and the correlation between the reduction in plasma lactate concentration and the increase in peak work rate in the PAV group of the study by HAWKINS *et al.* [62] is a marker of true physiological training effect. Other authors have confirmed benefits of addition of NPPV to pulmonary rehabilitation that were not observed with Heliox breathing [63, 64].

Why does NPPV sometimes fail? The study by BIANCHI *et al.* [61] found no additional benefit of assisted ventilation on exercise tolerance, dyspnoea and health status when compared with training alone. Moreover, the high rate of dropouts due to lack of compliance in the PAV group and the time spent to set the ventilator and to supervise the training session during assisted ventilation were practical drawbacks of the addition of mask PAV during a high intensity training programme, at least in that setting and in those patients with moderately severe stable COPD. Those results indicate it is not worthwhile to submit patients to unpleasant equipment (*e.g.* mask and related troubles), with the need of constant supervision of an individual operator to check for leaks, to reset the ventilator when needed and a substantial risk of lack of compliance. A potential complication of PAV is that its appropriate setting requires measurement of the patient's respiratory mechanics. In the study by BIANCHI *et al.* [61] PAV was set to the patient's comfort without any measurement of respiratory mechanics that otherwise would be impossible in a routine setting. In a study conducted in stable, chronically hypercapnic COPD patients, mask PAV, set at the patient's comfort, was able to unload ~70% of the total elastic load of the respiratory system but only 26% of the resistive burden [51]. Furthermore, it should be considered that patients' respiratory mechanics can change during exercise, for example due to increase of PEEPi [39], thus profoundly affecting the effect of NPPV. A change in PEEPi may affect the observed influence of PAV because PAV does not compensate for PEEPi. PAV, or any other inspiratory pressure assist, is not initiated until PEEPi is overcome, which is why exercise improves when PAV is superimposed upon CPAP. CPAP compensates for the threshold load while PAV compensates the elastic and resistive load of inspiration. Nevertheless, to explain the "negative" results of the study by BIANCHI *et al.* [61], the ventilatory demands of the exercising patients relative to the capacity of the ventilator must also be considered. Commercial ventilators often cannot accommodate the demand of an exercising COPD patient, which is why they may not comply. Furthermore, PAV during training may have limited role in the general population of COPD patients, many of whom have significant comorbidity.

Night-time NPPV and day-time exercise. There is another way to use NPPV to improve results of pulmonary rehabilitation. Patients with severe stable COPD were randomised by GARROD *et al.* [65] to home nocturnal NPPV and daytime exercise training or exercise training alone. After an 8-week training programme there was a significant improvement in mean shuttle walk test in the NPPV and exercise training group compared with the control group. The differences between the two groups became evident only in the final 4 weeks of the training programme. There was a significant improvement in HRQL. Only the NPPV group demonstrated a significant improvement in arterial oxygenation. Nocturnal NPPV is not necessarily directed at exercise and peripheral muscle adaptation. The main purpose is to correct night-time blood gases with a carryover through the day. The result should be an improvement in function including the ability to complete a daily exercise programme. This may be analogous to optimal pharmacological therapy.

Indeed the hypothesis that the observed increased exercise performance with nocturnal NPPV may be associated with increased quadriceps strength was not confirmed [66]. Quadriceps strength was measured as the twitch tension elicited by magnetic stimulation of the femoral nerve and the maximum voluntary contraction force in patients with chronic respiratory failure due to COPD and restrictive thoracic disease before and after 2-month NPPV. After NPPV there was significant clinical, arterial blood gas and walking distance improvement, but there was no improvement in quadriceps strength [66].

Methodological considerations

Any conclusion about the potential clinical utility of ventilatory assistance during exercise is difficult because of small study sample size, variability of pathophysiological abnormalities at study entry, differences in the ventilatory devices and operating characteristics of the ventilators, differences in pressure optimisation protocols, or lack of optimisation, differences in breathing circuit design with the potential for carbon dioxide rebreathing and differences in exercise protocols and evaluative methods of dyspnoea. Larger prospective controlled studies should be required to determine if ventilatory assistance will eventually be a useful adjunct to standard exercise protocols for dyspnoeic patients with more advanced cardiopulmonary diseases. The alternative is well-designed small samples regardless of positive or negative results. Replication of these studies will help guard against type I error. By replicating or repeating any experiment that is conducted with a "relaxed" significance level, the authors should be able to protect themselves from reporting a type I error while maintaining reasonable statistical power and sensitivity in an initial exploratory investigation. As in any study, large or small, a thorough description of subjects is required; the ability of the ventilatory device to meet the demands of the patient must be demonstrated; the operating characteristics described and carbon dioxide rebreathing must be within acceptable limits.

Electrical stimulation

Neuromuscular electrical stimulation (NMES) is used by physical therapists to improve muscle performance. This type of stimulation is characterised by a low-volt stimulation targeted to stimulate motor nerves to cause a muscle contraction. NMES has been used to increase healthy muscles performance [67, 68]. Application of NMES has been consistently associated with increased mass, strength, and endurance of both normally and abnormally innervated muscles in a range of pathological conditions [69–71]. In fact NMES retards muscle wasting during denervation immobilisation and optimises recovery of muscle strength during rehabilitation. It has been also used to assist respiratory function in patients with spinal cord injury [71–73]. There is growing evidence that NMES can be safely and effectively used in patients with skeletal muscle function deficit and exercise intolerance due to systemic diseases [74–77]. Low-frequency muscular electrical stimulation has been shown to induce an increase in the muscular oxidative capacities and could represent another form of mild physical training. It was well tolerated and induced an increased exercise capacity in patients with congestive heart failure, without undesirable increases in cardiac output. This form of training can be achieved at home and is local or loco-regional so it could be expected that it would not induce any adverse acute cardiac side-effect or late remodelling [74]. NMES treatment of thigh muscles using a combined NMES protocol comprising biphasic, symmetric, rectangular constant current impulses at different frequencies and amplitudes to enhance strength and endurance capacity appeared to be safe even in patients with heart failure and implanted pacemakers with bipolar sensing [78].

NMES and COPD. Pulmonary rehabilitation in active COPD patients may normalise the electrical activity of skeletal muscles during incremental dynamic exercise. The electromyographical signal confirms neuromuscular changes after endurance training [79]. Passive training of specific locomotor muscle groups by means of NMES might be better tolerated than whole body exercise in patients with severe COPD. It was hypothesised that this novel strategy would be particularly effective in improving functional impairment and the consequent disability that characterises patients with end stage COPD. Three small controlled studies of this technique in severe COPD patients have been reported [80–82]. Patients (mean $FEV1$ 38% pred) with advanced COPD were randomly assigned to either a home based 6-week quadriceps femoris NMES training programme or a 6-week control period before receiving NMES [80]. All patients were able to complete the NMES training programme successfully, even in the presence of exacerbations. Training was associated with significant improvements in muscle function, maximal and endurance exercise tolerance, and the dyspnoea domain of the Chronic Respiratory Disease Questionnaire [83]. Improvements in muscle performance and exercise capacity after NMES correlated well with reduction in perception of leg effort corrected for exercise intensity. Another randomised controlled trial of transcutaneous electrical muscle stimulation of the lower extremities was performed in stable patients (mean $FEV1$ 38% pred) [81]. Stimulation of the lower extremities was performed three times a week, 20 min each session, for six continuous weeks. Electrical muscle stimulation improved both the quadriceps strength (39.0% *versus* 9.0%) and hamstring muscle strength (33.9% *versus* 2.9%) in the treated and sham treated groups, respectively. The improvement in muscle strength carried over to better performance in the shuttle walk test in the treated group (36.1% *versus* 1.6% in the treated and sham groups respectively). There was no significant change in lung function, peak workload, or peak oxygen consumption in either group. Muscle stimulation was well tolerated by the patients with no dropouts and had >95% compliance with the protocol. NMES has also been applied in bed-bound COPD patients receiving mechanical ventilation with marked peripheral muscle hypotonia and atrophy. ZANOTTI *et al.* [82] compared the effects of active limb mobilisation with or without NMES on muscle strength, respiratory rate, heart rate, oxygen saturation, and time needed to transfer from bed to chair in two groups of bed-bound patients with chronic hypercapnic respiratory failure due to COPD who were receiving mechanical ventilation, with marked peripheral muscle hypotonia and atrophy. Patients were randomly assigned either to active limb mobilisation alone or to active limb mobilisation plus NMES. NMES was applied using square-wave alternate, symmetric, and compensated impulses for 30 min *b.i.d.* The duration of treatment was 28 days for all patients. Muscle strength improved significantly in the overall group of patients. Addition of NMES resulted in significantly improved muscle strength and respiratory rate and decreased the number of days needed to transfer from bed to chair. The major advantage of NMES over conventional exercise training is considered to be the lack of ventilatory stress during passive muscular activity, reflecting the reduced muscle mass involved.

Furthermore, one of these studies [80] indicates that NMES may be used even during periods of exacerbations, a condition associated with loss of muscle strength and mass [84].

However, there are negative studies in which no significant change in neurophysiological, aerobic performance or clinical status occurred after electrostimulation [85, 86]. Furthermore, studies in COPD may have limitations: *e.g.* a sham/placebo was not included in the study by NEDER *et al.* [80], patients observed are limited, therefore these studies must be considered as preliminary, and NMES should be still considered as an experimental tool in pulmonary rehabilitation. Further studies are necessary to include this modality in routine pulmonary rehabilitation programmes. In particular, further randomised trials using larger samples and longer follow-up periods are needed. Optimal forms of stimulation settings are yet to be determined, as are possible sex-related differences in responsiveness to electrical stimulation. For example, in a study in normal subjects muscle torque and fatigue of electrically induced contractions depended on the waveform used to stimulate the contraction, with monophasic and biphasic waveforms having an advantage over the polyphasic waveform [87]. Morphological studies correlating improvements in exercise tolerance with muscular changes described with conventional exercise training are also needed [25, 26].

Interval training

Interval training is characterised by repeated bouts of high-intensity exercise interspersed with recovery periods (light exercise or rest) [88]. In healthy subjects, interval training with rest during the recovery period has been widely studied and, in some studies, has shown better results than continuous training [88–93]. GOROSTIAGA *et al.* [89] showed a greater increase in peak oxygen consumption and peak work rate after an interval training programme than after continuous training. GAESSER and WILSON [90] showed that peak oxygen consumption increased significantly only with interval training and POOLE and GAESSER [91] showed that the lactate threshold exhibited greater improvements in interval training than in continuous training. AMAIDI *et al.* [92] found that, in elderly people, interval training was more easily accepted and tolerated than continuous training. Theoretical explanations for superior responses to interval training have been proposed. High intensity work rate for 1 or 2 min induces high blood lactate levels due to the depletion of phosphocreatine and the use of oxygen myoglobin-bound reserves, but interspersed periods of sub-lactate threshold work rates may facilitate lactate removal [88]. When compared with the same total amount of work performed continuously, interval training has been shown to induce less lactate accumulation [93] and to prevent glycogen depletion by favouring the metabolism of lipids [88].

Interval training in COPD. In patients with COPD, interval training has been shown capable of inducing physiological training effects [14, 94–100]. The most common interval training protocol studied in these patients is moderate to high intensity exercise alternated with low-intensity exercise [96, 98–102]. Rehabilitation programmes, including interval training, resulted in delay in lactate threshold, increase in peak work rate and peak oxygen consumption and improvements in HRQL [96, 98]. After an interval training programme, an increase in peak oxygen extraction ratio, reduced phosphocreatine recovery time and improved cellular bioenergetics have been shown [101]. Nevertheless, the superiority of high-intensity bilevel interval over moderate-intensity continuous training was not clearly demonstrated by COPPOOLSE *et al.* [97].

Oxygen supplementation

Supplemental oxygen has the potential to increase exercise tolerance of the hypoxaemic COPD patient by different mechanisms: hypoxic stimulation of the carotid bodies is reduced, the pulmonary circulation vasodilates and arterial oxygen content increases. The latter two mechanisms may potentially reduce carotid body stimulation at heavy levels of exercise by increasing oxygen delivery to the exercising muscles and reducing carotid body stimulation by lactic acidaemia. The main mechanism for oxygen's effect on exercise tolerance has recently been clarified [103]. Ambulatory oxygen therapy has widely been shown to increase exercise performance and to relieve exercise breathlessness in COPD patients [104–108]. Recent studies indicate that reduction in hyperinflation plays an important role in the oxygen-related relief of dyspnoea [104, 108]. Interestingly, supplemental oxygen generally increases exercise tolerance in patients with only mild to moderate hypoxaemia (*i.e.* levels of hypoxaemia not severe enough to meet guidelines for LTOT) [104, 109, 110].

Despite these positive physiological results, a study by TERRADOS *et al.* [111], suggests that mild hypoxaemia accelerates peripheral muscle adaptation such that the use of supplemental oxygen during training of mildly hypoxaemic patients may not be advantageous. This seems to have been confirmed by previous studies of COPD patients trained while using supplemental oxygen. These studies failed to demonstrate benefits of supplemental oxygen during rehabilitation [112–116]. A recently published double blind study involved nonhypoxaemic patients with severe COPD (FEV1 36% pred) exercised in a 7 week outpatient programme [117]. During exercise they received by nasal cannula either oxygen (3 L·min^{-1}) or compressed air (3 L·min^{-1}). Exercise was on cycle ergometers for 45 min, 3 times per week; as the programme proceeded work rate was progressively increased. Both groups had higher exercise tolerance (while breathing air) after training. However, the oxygen trained group increased training intensity more rapidly over the 7 weeks than the control group. After training, exercise endurance increased significantly more in the oxygen trained group (213%) than in controls (170%). This study [117] differed somehow from others [112–116]. Indeed in this study [117] sufficient supplemental oxygen was given during training to raise arterial oxygen saturation, subjects were urged to maximise their training work rates so that any increase in exercise tolerance produced by oxygen breathing would result in higher training intensity and both effort dependent and effort independent measures of exercise tolerance were utilised to detect the magnitude of the training effect. Nevertheless, other studies have achieved increases in oxygen uptake with high intensity training without supplemental oxygen [118]. Further studies are needed to define the appropriate patients in order to generalise such intervention. In the light of the present knowledge oxygen supplementation during training should be limited to individual cases.

Biofeedback

Biofeedback refers to techniques to teach self-control over physiological functions. In other words people might be taught to increase or decrease the activity of internal bodily functions. The most common application of biofeedback has

been stress management by teaching major muscle groups relaxation. More recently using biofeedback patients have tried to modify such autonomic functions as vasomotor activity, heart rate, blood pressure, and bronchomotor tone. Several biofeedback techniques have been applied to patients with pulmonary disorders in a frame of pulmonary rehabilitation programmes. In respiratory biofeedback a signal relating to some respiratory function is monitored and displayed to the patient, who tries to modify that function. Biofeedback has been used in patients with asthma, emphysema, and pulmonary fibrosis and has been used to improve gas exchange and reduce the WOB [119]. Techniques varied from relaxation and stress management to patient self-control. Electromyography, incentive spirometry, airway resistance signals and pulse oximetry have been used [119, 120]. Training the patient in pursed-lips breathing guided by oximetry, and decreasing the time of weaning from mechanical ventilation are examples of biofeedback application to respiratory patients [121, 122]. Application of biofeedback to exercise in COPD patients has been less studied. In a study by COLLINS et al. [123] to determine the effects of biofeedback during exercise training of COPD, the authors concluded that exercise training with biofeedback and exercise training alone were equally effective in improving leg-cycle exercise tolerance in patients with moderate-to-severe COPD. However, the inability to conclude an improvement with biofeedback combined with exercise training over exercise training alone may have been due to lack of statistical power. Clearly this issue does require further investigation.

Final considerations

The positive conclusion from the above studies is that multidisciplinary pulmonary rehabilitation in its consolidated "old" modalities, as evaluated by evidence based medicine is a valuable adjunct to treatment of chronic obstructive pulmonary disease [3, 5, 8–11]. In this frame exercise training is a cornerstone. The value of studies supporting the use of these newer strategies in the clinical management of chronic obstructive pulmonary disease patients differs substantially among these techniques. Indeed, clinical trials designed to establish that a given intervention yields superior results compared with standard interventions are generally difficult to perform because of the rather wide variability of responses to exercise interventions among chronic obstructive pulmonary disease patients. While high intensity training may be useful to induce a true physiological response to training, it does not necessarily translate into better health-related quality of life compared with low intensity training. Nevertheless, this does not mean that patients would not have benefited from a more intense exercise programme and improved cardiopulmonary capacity. Therefore, there is a theoretical reason to go on with research in tools to increase exercise intensity patients can tolerate. Furthermore, the modalities discussed should be used as adjuncts to a well-designed comprehensive respiratory rehabilitation programme including other interventions, such as education, nutrition, and psychological counselling.

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