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Review Article

Non-invasive Ventilation as an Adjunct in Pulmonary Rehabilitation in Stable COPD Patients

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Abstract

Pulmonary rehabilitation (PR) is a non-pharmacological intervention addressed to chronic obstructive pulmonary disease (COPD) and non-COPD chronic respiratory patients, a key management strategy scientifically demonstrated to improve exercise capacity, dyspnoea, health status and psychological wellbeing. The main body of literature comes from COPD patients, as they provide the core evidence for PR programmes. PR is recommended to moderate and even to severe patients having chronic respiratory failure; their significant psychological impairment and potential for greater instability during the PR programme will be carefully considered by the multidisciplinary team. Patients who already receive long-term domiciliary non-invasive ventilation (NIV) for chronic respiratory failure might exercise with NIV during exercise training if acceptable and tolerable to the patient.

Keywords: *Non-Invasive Ventilation; Pulmonary Rehabilitation; Chronic Obstructive Pulmonary Disease*

Abbreviations

ACPV: Assist Pressure Control Ventilation; COPD: Chronic Obstructive Pulmonary Disease; CPAP: Continuous Positive Airway Pressure; CHRF: Chronic Hypercapnic Respiratory Failure; EFL: Expiratory Flow Limitation; EPAP - Expiratory Positive Airway Pressure; FOT: Forced Oscillation Technique; HMV: Home Mechanical Ventilation; HRQoL: Health-Related Quality of Life; IPAP: Inspiratory Positive Airway Pressure; LTOT: Long-Term Oxygen Therapy; NIOV: Non-Invasive Open Ventilation; NIV: Non-Invasive Ventilation; NPPV: Non-Invasive Positive Pressure Ventilation; NPV: Negative Pressure Ventilation; PA: Physical Activity; PAP: Positive Airway Pressure; PAV: Proportional Assist Ventilation; pNIV: Portable Non-Invasive Ventilation; PR: Pulmonary Rehabilitation

Introduction

Briefly about pulmonary rehabilitation

COPD is a leading cause of morbidity and mortality, with an increased burden of disease worldwide and constitutes a major healthcare burden [1,2]. Of all most prevalent illnesses, only COPD is on rise, being currently the third cause of death after ischaemic heart disease and stroke. Pulmonary cellular inflammation is accompanied by extensive airway remodelling and parenchymal destruction, which lead to progressive breathlessness and chronic airflow obstruction [3,4]. COPD is known to induce, apart from respiratory symptoms, a decrease in muscle strength and endurance due to systemic inflammation, vulnerability to fatigue and a decline in exercise capacity and cardiac function [4-7]. A decrease in physical activity and the consecutive sedentary life, along to the weakened pulmonary function, will result in a vicious cycle with decline in HRQoL and physical ability at a disproportionate rate comparing to the decline of lung function [5]. Therefore, COPD has extensively been reported as a complex disease affecting patients' health beyond the lungs with a variety of intrapulmonary and extrapulmonary components and considerable variability between individuals [8].

Pulmonary rehabilitation is described as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour changes, designed to improve the physical and psychological conditions of people with chronic respiratory disease, and to promote long-term adherence to health-enhancing behaviours" [9]. The main goal for PR programmes is to enhance physical activity (PA) towards normal levels, to return the patient to the highest possible capacity in order to achieve the maximum level of independence and functioning in the community [8]. Despite being a cost-beneficial intervention, approximately two-fifth of chronic respiratory patients have been informed by their health care provider about PR and its positive results. This might be an explanation why < 2% of the patients are referred to some sort of rehabilitative intervention [10].

The main body of evidences are coming from COPD patients, but PR is effective as well in many others obstructive and restrictive conditions. Multidisciplinary PR is a key component in the management of COPD [1] and has proved to be beneficial in patients with COPD in terms of exercise capacity, symptoms and health-related quality of life (HRQoL) [11,12]; other short-term benefits are improving the mood, and reducing the breathlessness and health care utilization, being one of the most cost-effective therapeutic strategies [1,4]. PR is recommended for all symptomatic patients, regardless the severity of disease, but recommendations are stronger in moderate-to-severe COPD. PR is addressed to stable patients, after an acute exacerbation, in intensive care unit, in the perioperative period after a lung transplantation, before and after lung cancer surgery, and before endobronchial lung volume reduction [4]. It can be offered in a hospital-based outpatient setting, in an inpatient setting, a community-based setting and at the patient's home [10]. The longer the duration of the PR programmes (up to 12-wk), the greater sustained benefits in comparison with the shorter ones [11].

These benefits tend to wane over time and most measures of improvement return to baseline by 12 - 24 months [1,11]. Therefore, experts recommend continuation of exercise training beyond initial PR in order to prevent a decline in exercise capacity [11]. Maintenance programmes may consist in simple techniques used in ambulatory, community or home programmes [11]. Home-based exercise interventions are safe and beneficial, helpful for patients who lack access to or are unable to participate in centre-based PR programmes [13]. The key to maintain benefits is to reduce sedentary behaviour, and promote real change in life habits, enhancing PA in patients after completing a PR programme [11,14]; the increase on PA derives from factors around the patients, like an active spouse, walking the dog and other pets, and grand parenting [13].

Non-invasive ventilation

In advanced stages of respiratory disease, patients frequently develop chronic hypercapnic respiratory failure (CHRF). NIV is the standard treatment for patients with CHRF due to restrictive lung disease and COPD, and a major indication for home mechanical ventilation (HMV) in Europe [2]. In patients with COPD and CHRF, chronic NIV has led to clinically relevant improvements in terms of dyspnoea, gas exchange, lung function, HRQoL, hospital admission and survival [2,15,16], when high enough respiratory pressures and back-up respiratory rates were applied.

In high-pressure NIV may develop a haemodynamic compromise due to reduced venous return from high intra-thoracic pressures. These factors may affect results of NIV in NIV-naïve patients or in those with compromised cardiac performance [15]. Still, as shown by Dreher., *et al*. high intensity NPPV using a controlled mode of ventilation with a mean inspiratory pressure of 29 mBar is well tolerated by COPD patients with hypercapnic respiratory failure. Hence, high-intensity NPPV is superior to low-intensity NPPV using an inspiratory pressure of 15 mBAR in controlling nocturnal hypoventilation in this population of patients [17]. It is also advantageous in improving dyspnoea during physical activity, lung function and HRQoL [17]. They have been reported two disadvantages of high-intensity NPPV:

patients need more days in hospital to acclimatise and there is an increased expiratory leakage [17] comparing to low-intensity NPPV. Recent pulmonary rehabilitation guidelines [18] suggest that NIV during exercise training should be offered to patients who already receive domiciliary NIV. With increased use of high-pressure NIV for home therapy, the use of NIV during PR would become more feasible.

Non-invasive ventilation as an adjunct to pulmonary rehabilitation

NIV may be used as an adjunctive therapy to PR that unloads the respiratory muscles with the aim to increase the intensity of exercise training in selected patients with severe chronic respiratory disease who have a suboptimal response to exercise [9]. The benefits appear to be more marked in patients with severe COPD, and higher tolerated positive pressure may lead to greater improvements [9], with improved exercise performance and reduced dyspnoea [19]. Long-term oxygen therapy (LTOT) and non-invasive ventilation (NIV) are potentially valuable therapeutic options, especially in COPD patients with severe lung hyperinflation and exercise-induced desaturation noticed during exercise training as part of a comprehensive PR programme [13]. The addition of nasal positive pressure ventilation to LTOT in hypercapnic patients has been shown to improve arterial blood gases, dyspnoea, quality of life and survival [16,19]. Oxygen supplementation in moderate to severe COPD patients can acutely increase exercise capacity, the amount of training they can undertake, and thus the benefits of PR. Alleviation at a certain extend of ventilatory limitation will allow greater cardiac and muscular stress, with further beneficial effects on stroke volume and oxygen extraction [18]. SpO_2 should be > 88% during exercise; if SpO_2 is ≤ 88% while breathing room air, supplemental oxygen should be used to maintain SpO_2 at > 88% [7,20] or > 90% according to other authors [21,22].

COPD is characterized by recurrent exacerbations leading to episodes of severe clinical deterioration requiring hospitalization and ventilatory support. Persistent hypercapnia after an episode of AECOPD is associated with excess mortality and early hospitalization [23]. That means extra costs for caring same patients; therefore, it is an urgent need for measures to prevent readmissions in this area. Non-invasive positive airway pressure (PAP) interventions, applied during exercise, at rest and in the end-of-life setting, can be used to restore the balance of respiratory muscle load and capacity, with reducing neural respiratory drive and dyspnoea [24].

Discussion

Usefulness of non-invasive ventilation during pulmonary rehabilitation in stable COPD patients

Exercise capacity is significantly reduced in patients with COPD and chronic hypercapnia. Reduced ventilatory capacity combined with an increased ventilatory load leads to intolerable dyspnoea at low level of exercise [25]. Therefore, NIV was proposed as an adjunct to PR in patients with severe COPD in order to allow the patients to exercise at a higher training intensity and to obtain a greater effect compared to exercise training without NIV [15], with both improvement in physical functions and exercise performance [5]. In majority of studies have been used relatively low to moderate levels of inspiratory pressure during exercise, and the optimal mode and settings in a population with very severe lung disease is still unknown [15,25]. A Cochrane review performed in 2014 by Menadue., *et al*. has shown that NIV during exercise training may allow COPD patients to exercise at a higher training intensity and to achieve a greater physiological training effect compared with exercise training alone or exercise training with sham NIV [26]. It is currently unknown if the demonstrated benefit of NIV during exercise training is clinically worthwhile or cost-effective [26].

NIV is used during PR courses in COPD patients with hyperinflation and exercise induced desaturation [8], directly during exercise to unload respiratory muscles, optimize pulmonary mechanics and alleviate the effects of respiratory limitations, facilitating an enhanced training effect. The addition of non-invasive positive pressure ventilation (NPPV) to an exercise training programme in severe COPD cases has benefits in terms of exercise tolerance and HRQoL comparing to exercise training alone [19]. There are difficulties in administration of nasal positive pressure ventilation during physical training, but nocturnal domiciliary NIV provided in conjunction with PR programme will lead to greater improvements in exercise capacity, health status, inspiratory muscle strength, alveolar ventilation and arterial oxygenation, together with improving sleep quality in hypercapnic COPD patients [19]. In a study conducted by Garrod., *et al*. the median IPAP was 16 cmH_2O [13-24] and the median EPAP was 4 cmH_2O [4-6]. There are reported some reasons for poor compliance like upper airway problems, complaints regarding disturbance to spouse and inability to sleep due to ventilator noise [19].

Another recommendation is at night in patients with chronic respiratory failure, to improve their clinical status during the exercise programme, functional capacity, HRQoL and sleep quality [24,27]. The benefits are achieved through optimization of the respiratory muscle load-capacity-drive relationship [24]. NIV delivered during exercise enables patients with severe COPD to exercise at higher intensity, to increase their exercise endurance time and walking distance [24,27]. NPPV is a feasible and beneficial tool in hospital-based PR [27], but clinical application of NIV during physical exercise is limited by time consuming NIV setup, need for specialist supervision, limited portability of devices and the ventilator model, battery duration and poor patient tolerance [24,28].

NIV prolongs endurance during exercise in COPD, but routine use is difficult. Recently, handheld, battery operated and portable NIV (pNIV) devices, providing pressure support ventilation, require the patient to inspire and expire through a mouthpiece, are intended to be applied at the end of exercise to reduce the time to return at baseline respiratory status in COPD patients, thus acting as dyspnoea-relief tools. They provide an accessible and acceptable method to improve exercise capacity and relieve exertional breathlessness by reducing dynamic hyperinflation and leg discomfort, together with improving cardiac output, systemic oxygen delivery and exercise endurance time [24,29].

Portable NIV devices are primarily intended to aid recovery from breathlessness after activities in daily life. Additionally, they offer benefit within PR courses, especially in intermittent/interval training regimens [29]. VitaBreath provides positive inspiratory pressure support to reduce the work of breathing and positive expiratory pressure support to keep the airways open during expiration and reduce the air trapping [29]. It was shown that exercise-induced dynamic hyperinflation normally persists several minutes after the end of exercise [29], making the use of pNIV rationale and recommended. A technical limitation of these devices is that the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) are fixed. Excessive EPAP can worsen hyperinflation and circulatory limitations. The fixed pressures may be sub-optimal in some patients; therefore, the future devices should have the ability to adjust EPAP, making the pressure support more desirable and potentially automated [29]. Future studies should investigate the additive effect of oxygen supplementation to intermittent NIV support during conventional PR [29].

Clinicians have to establish the inspiratory positive airway pressure, that unload respiratory muscles and increase tidal volume, and the EPAP to an optimal level, to prevent the airway expiratory closure and abolish the expiratory flow limitation (ELF), leading to a reduction in respiratory neural drive and breathlessness [24]. In clinical practise, EPAP is estimated for COPD patients by clinical judgement, as specialists in NIV are not always available. The forced oscillation technique (FOT) that detects respiratory system impedance by delivering sound waves through a mouthpiece or facemask, has recently been developed to detect ELF during tidal breathing in COPD patients treated by NIV. FOT was incorporated into novel PA devices to auto-titrate EPAP continuously to the optimal pressure where ELF is abolished, the work of breathing, neural drive, and inspiratory threshold are minimized [24].

Less practical in daily life but providing a greater improvement in exercise tolerance are the continuous positive pressure support devices like continuous positive airway pressure (CPAP), inspiratory pressure support including proportional assist ventilation (PAV), and non-invasive "open" ventilation (NIOV) [12,25,29]. All these ventilation support strategies provide continuous unloading of the respiratory muscles and reduce the work of breathing [29], thus reducing dyspnoea and enhancing exercise tolerance in COPD patients [12]. Inspiratory pressure support strategies used during exercise increase endurance, reduce dyspnoea, unload the respiratory muscles and sustain exercise induced lactataemia for longer [25,30].

Portable CPAP devices, light-weighted and battery-powered, are very useful in cases with excessive dynamic airway collapse where they provide a pneumatic stent to maintain airway patency, reduce expiratory resistance and improve expiratory airflow [24]. After providing PAV to a group of patients with more severe COPD during a supervised high-intensity out-patients cycle exercise programme, mean training and peak work rate was higher in this group. Iso-worked lactataemia after training was reduced in the PAV assisted group more than in the unassisted group [12,25]. PAV is a mode of ventilation that matches ventilator output to patient effort, allowing the patients to prolong exercises and to achieve greater improvements in exercise performance [25]. NIOV system (BT-V2S Breath Technologies) operating in conjunction with a portable oxygen tank was found to decrease respiratory muscle activation and dyspnoea, and to improve cycle ergometer exercise tolerance; it is a light, wearable 1-lb ventilator, practical for facilitating activities of everyday living [31]. They have been compared the effects of high-intensity training with mouthpiece inspiratory pressure support delivering 10 cmH_2O with 5 cmH_2O. IPS10 resulted in significantly larger improvements in exercise endurance than training with IPS5 in moderate-to-severe COPD patients. Therefore, it is suggested that IPS10 may be considered as adjunct during high-intensity training through better unloading the inspiratory muscles during exercise [32].

Some centres use Assist Pressure Control Ventilation (APCV) mode with a high backup rate, intending to achieve controlled ventilation. The use of APCV mode during exercise implies to bet set up a minimum mandatory backup rate along with a fixed inspiratory time for both patient and machine-triggered breaths. The aim is to provide optimal respiratory muscle unloading and gas exchange during exercise. There is the possibility to worsen the dynamic hyperinflation if inspiratory time is set inappropriately long, particularly if the exercise spontaneous respiratory rate increases during the exercise period [15].

The use of non-invasive positive pressure ventilation (NPPV) during training has a limited role on a routine basis. There are only small study sample size, variability in pathophysiological abnormalities at study entry, differences in the ventilatory devices and operation characteristics of the ventilators, in pressure-optimisation protocols or lack of optimisation, in breathing-circuit design with the potential for carbon dioxide rebreathing, in exercise protocols and evaluation dyspnoea methods [12]. A practical issue raised by high-intensity exercise training is the use of facemask or mouthpiece. In these conditions, patients may breathe through the mouth rather through the nose, thus requiring a face mask or a mouthpiece, but compliance to a face mask may not be easy during physical training [12]. Larger prospective controlled studies should be required to determine the usefulness of ventilatory assistance as an adjunct to standard exercise protocols for dyspnoeic patients with more advanced cardiopulmonary diseases [12].

Negative pressure ventilation (NPV), when used as an adjuvant to PR, improves lung function, increases exercise capacity, prolongs survival and reduces exacerbations in COPD patients with exercise desaturation, who have an increased mortality risk compared with non-desaturating COPD patients. The NPV group had a slower yearly decline in lung function and in 6-minute walking distance, irrespective with exercise desaturation [3]. Maintenance of NPV reduces long-term mortality in COPD patients, irrespective of the presence of desaturation during the 6MWT. Huang., *et al*. [3] have established a hospital maintenance NPV programme that included NPV support, breathing training and an educational programme (relaxation techniques and a home pacing walking exercise) in daily clinical practice. Breathing training consisted of pursued-lipped, controlled and diaphragmatic breathing. The patients received NPV with breathing training via a cuirass ventilator (cuirass diameter 21 or 34 cm) for 60 minutes, once per week, at least three times per month. Patients with baseline saturation less than 90% have received oxygen supplementation [13]. The mechanism of the beneficial effects of NPV in Huang., *et al*. study is unclear and may result in part from reduced dead space or decreased respiratory muscle load [13].

Conclusion

Relatively small studies have shown the benefits of negative or positive non-invasive ventilation. In severe hypercapnic patients, these ventilators are a hope that should be gradually developed and worldwide provided.

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