Is there enough room for non-invasive ventilation in pulmonary rehabilitation?

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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 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. Optimizing medical management (eg, inhaled bronchodilators, oxygen therapy, non-invasive ventilation) may enhance the results of exercise training. 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. It is not advisable to offer long-term domiciliary NIV with the only aim to improve outcomes during PR course. There are different attempts to use both negative and positive NIV in limited clinical studies. Long-term adherence to exercise is an important goal of PR programmes and teams, targeting to translate all-domain gains of PR into increased physical activity and participation to real life. Being a reliable alternative for the future, studies should focus on pressure regimens, type of devices, acceptability and portability for everyday activities.

Key words: chronic obstructive pulmonary disease, pulmonary rehabilitation, non-invasive ventilation

Abbreviations

AECOPD – acute exacerbation of chronic obstructive pulmonary disease
BIPAP – bilevel positive airway pressure
COPD – chronic obstructive pulmonary disease
CPAP – continuous positive airway pressure
CHRF – chronic hypercapnic respiratory failure
EPAP - expiratory positive airway pressure
FEV1 – forced expiratory volume in 1 second
GOLD – The Global Initiative for Chronic Obstructive Lung Disease
HOT-HMV – home oxygen therapy and home mechanical ventilation
HMV – home mechanical ventilation
HRQoL – health-related quality of life
ICU – intensive care unit
LTOT – long-term oxygen therapy
MIE – mechanical insufflation-exsufflation
6MWT – six-minute walking test
NIV – non-invasive ventilation
NPPV – non-invasive positive pressure ventilation
NPV – negative pressure ventilation
PaCO2 – arterial partial pressure of carbon dioxide
PAP – positive airway pressure
PAV – proportional assist ventilation
pNIV – portable non-invasive ventilation
PR – pulmonary rehabilitation
SpO2% - saturation of arterial blood with oxygen measured by pulse oximetry

The concept of pulmonary rehabilitation briefly

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 change, designed to improve the physical and psychological condition of people with chronic respiratory disease, and to promote the long-term adherence to health-enhancing behaviours” [1]. The main goal for PR programmes is to enhance physical activity 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 [2, 3]. Despite being a cost-beneficial intervention, only 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 one of the available PR programmes [4]. The main body of evidences are coming from the COPD patients, but PR is effective as well in many others obstructive and restrictive conditions.

COPD is a leading cause of morbidity and mortality, with an increased burden of disease worldwide and constitutes a major healthcare concern [5, 6]. COPD patients are referred to PR due to persistent respiratory symptoms and/or limited activities of daily living and an unsatisfactory response to medical treatment offered in primary care [7]. PR addresses breathlessness, the perceived discomfort of breathing, a common symptom too many respiratory and systemic diseases [8]. Breathlessness is the consequence of imbalance between the increased respiratory muscle load and reduced ventilatory capacity [8]. Neural respiratory drive, the electrical output from the brainstem to the respiratory muscles, increases in response to this imbalance and acts to maintain an appropriate ventilation, thus becoming a major contributor to the subjective breathlessness [8, 9]. Breathlessness occurs in COPD, with disease advancement or in an AECOPD as a result of imbalance in the load-capacity-drive relationship of the ventilatory system [8], with dynamic hyperinflation and impaired gas exchange that worsen ventilation-perfusion mismatch [10].

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 [9, 11, 12, and 13]. A decrease in physical activity and the consequent sedentary life, along to the weakened pulmonary function, will result in a vicious cycle with decline in health-related quality of life (HRQoL) and physical ability at a disproportionate rate comparing to the decline of lung function [11]. Therefore, COPD has extensively been reported as a complex disease affecting patients’ health beyond the lungs with multiple intrapulmonary and extra pulmonary components and considerable variability between individuals [2].

Multidisciplinary PR is a key component in the management of COPD [5], and has proved to be beneficial in patients with COPD in terms of improving exercise capacity, symptoms (as breathlessness, fatigue, and mood) and HRQoL [14, 15]; it reduces health care utilization, being one of the most cost-effective therapeutic strategies [5, 12]. PR is addressed to stable patients especially with moderate-to-severe disease, after an acute exacerbation, in intensive care unit, in perioperative period after a lung transplantation, before and after lung cancer surgery, and before endobronchial lung volume reduction [12]. It can be offered in a hospital-based outpatient setting, in an inpatient setting, a community-based setting and at the patient’s home [4].

Large differences in results may arise from exercise type, level of supervision, education and physiotherapy strategies, psychological support, use of medication and mostly of duration and frequency of the maintenance programmes [14]. The longer the duration of the PR programmes the greater sustained benefits in comparison with the shorter ones [14]. A contribution may have the patients’ adherence to the programme, severity of disease, comorbidities, and accessibility of the PR premises [14]. These benefits tend to wane over time and most measures of improvement return to baseline by 12-24 months [5, 14]. Therefore, experts recommend continuation of exercise training beyond initial PR in order to prevent a decline in exercise capacity [14]. Maintenance programmes may consist in simple techniques used in ambulatory, community, or home programmes [14]. 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; the increase on PA derives from factors around the patients, like an active spouse, walking the dog and other pets, and grand parenting [16].

Exercise training is the cornerstone in PR programmes and the best approach for increasing muscle strength, decreasing symptoms, reducing mood abnormalities, improving cardiovascular function and the motivation for physical activity [12]. The target training intensity in the PR exercise setting is critically dependent on baseline exercise testing, which is associated with a learning effect [16]. The main components of exercise training programmes are endurance and resistance training that should be practised supervised at least twice weekly, more than 60% to 80% of the maximal work rate, delivered as high-intensity and dynamic, interval and continuous training [9, 12, 13, 17]; in parallel with these supervised sessions, there are recommended five unsupervised sessions of 30 min of PA per week, in line with standard healthy living advice [17]. Typical modes of aerobic exercise are walking or cycling [13]. In stable COPD patients, a combination of endurance and resistance training should be performed to maximize improvement in limb muscle function and whole-body exercise capacity [9].

**Non-invasive ventilation or why to think about it**

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 COPD and restrictive lung diseases, and a major indication for home mechanical ventilation (HMV) in Europe [6]. COPD patients benefit from NIV once they have COPD GOLD stage III or IV and CHRF (PaCO₂ > 6.0 kPa) in a stable clinical condition. Recent pulmonary rehabilitation BTS guidelines [17] 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.

In patients with chronic hypercapnic respiratory failure, long-term non-invasive positive pressure ventilation (NPPV) improves important physiological variables such as blood gases and lung hyperinflation. Results from clinical studies have shown that NPPV improves exercise capacity, exercise-related dyspnoea, pulmonary cachexia, sleep quality and QRoL. Moreover, NPPV treatment might be associated with fewer hospital admission and lower overall treatment costs [18]. The best results with long-term NPPV have been noticed in studies using more intensive forms of NPPV, with higher inspiratory pressures and high back-up frequencies that have improved or even normalised hypercapnia [6, 18, 19, and 20].

Köhnlein et al have conducted a study in 2014 with the intention to assess survival in chronic hypercapnic COPD patients using NPPV in addition to standard treatment for at least 6 hours at night and anytime during daytime. The results provided evidence that NPPV addition in a group of stable COPD patients reduces hypercapnia, improves overall survival, exercise capacity and HRQoL over 1 year when comparing with guideline-oriented COPD treatment without NPPV [18]. In the study conducted by Raveling et al in 2018, NIV was initiated in COPD patients in a stable condition and after an episode of acute respiratory failure using BiPAP ventilators [6]. Compliance to the ventilator after 3 months was 6.6 ± 2.0 hours per night and 80% of the patients have used NIV for more than 5 hours per night. A higher body mass index and forced expiratory volume in one second, a lower bicarbonate before NIV initiation, younger age and NIV initiated in stable conditions were independently associated with better survival [6].

In high-pressures, 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 [19]. 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 [21]. It is also advantageous in improving dyspnoea during physical activity, lung function and HRQoL [21]. 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 comparing to low-intensity NPPV [21].

**Types of non-invasive ventilators**

**Negative airway pressure devices**

Techniques to deliver ventilatory support have developed in 19th century and became popular during the polio epidemic in early 20th century [8]. There are two types of negative pressure ventilation (NPV). One is tank ventilation that provides intermittent sub-atmospheric pressure around the whole body. The other one is cuirass ventilator that provides negative pressure around the chest only and creates a gradient pressure between thorax and lower body, which may increase intrathoracic venous return, right cardiac output and lung perfusion [22]. Breathing pattern undergoing cuirass ventilator is a real approximation of the normal physiological breathing, with more natural distribution of air in the lungs. Hence, NPV does not restrict the patients’ activities and they can be more comfortable [22].

**Positive airway pressure devices**

Positive airway pressure (PAP) devices offer today a consistent solution; they unload respiratory system and increase its capacity, with a consecutive reduction in neural respiratory drive and breathlessness [8]. Limitation of negative pressure devices promoted development of PAP devices to deliver continuous positive airway pressure (CPAP) and bi-level pressure support. CPAP delivers a fixed level of positive airway pressure during the whole respiratory cycle [8]. Bi-level pressure support, known as NIV, delivers a positive pressure during expiration and a higher positive pressure during inspiration to support inspiratory effort. PAP devices deliver respiratory support through oronasal or nasal mask interfaces, and not through endotracheal tube or tracheostomy, thus being considered as non-invasive devices [8]. PAP devices have well established benefits in acute and chronic respiratory failure in a large range of conditions, including COPD, obstructive sleep apnoea, obesity-related respiratory failure, progressive neuromuscular disease (NMD) and cardiogenic pulmonary oedema, through restoring respiratory muscles load-capacity balance, promoting alveolar ventilation and improving gas exchange [8].

**Non-invasive ventilation act 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 [1]. The benefits appear to be more marked in patients with severe COPD, and higher tolerated positive pressure may lead to greater improvements [1], with improved exercise performance and reduced breathlessness [23]. 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 [24]. 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 [8].

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 [16]. For patients with COPD and chronic hypoxia LTOT is crucial in terms of improving survival. In these cases, use of supplemental oxygen during exercise may be associated with reduced exertional SpO2 and increased exercise performance [25]. 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 [20, 23]. Oxygen saturation measured by pulse oximetry (SpO2) should be > 88% during exercise; if SpO2 is ≤ 88% while breathing room air, supplemental oxygen should be used to maintain SpO2 at > 88% [13, 26] or > 90% according to other authors [22, 27].

**In AECOPD**

COPD exacerbations are known to deteriorate life quality, to enhance disease progression and increase mortality [12]. Acute respiratory failure leading to acute or acute-on-chronic respiratory acidosis, develops when the respiratory muscles fail to achieve adequate alveolar ventilation despite high levels of diaphragmatic activity [28] and when appear alterations in central ventilatory control [18]. The official European Respiratory Society/American Thoracic Society clinical practical guidelines suggest to consider bi-level NIV in patients with AECOPD in three clinical settings: to prevent acute respiratory acidosis; to prevent endotracheal intubation and invasive mechanical ventilation in patients with mild to moderate acidosis and respiratory distress; and as an alternative to invasive ventilation in patients with severe acidosis and more severe respiratory distress [28]. Bi-level NIV is known to improve related symptoms, and to reduce the length of hospital stay, intubation rate and mortality rate [11, 28]. NPPV is a life support intervention that does not require sedation, allowing the patients to communicate with the family and caregivers during the interruptions, to eat, to drink and to take decisions regarding their care. The outcomes were more favourable in COPD patients with strong cough and awake [29, 30].

The British Thoracic Society recommends the initiation of early PR within 1 month of hospital discharge after exacerbation, consisting of a minimum of twice a week supervised session, lasting between 6 to 12 weeks [17]. PR can be delivered late post-exacerbation that is 6 months after COPD exacerbations, the majority flare ups requiring hospitalisation or hospital at home services [17]. More recently, a reliable group of experts have strongly recommended the initiation of PR during and shortly after an exacerbation-related hospitalisation, as this results in clinically relevant improvements in exercise performance, lower-limb muscle function, balance and quality of life compared to usual care [31]. NIV can improve exercise tolerance with less desaturation in patients admitted to hospital with an exacerbation of chronic respiratory disease, but participation is limited in older populations; it is more suitable in younger patients with fewer comorbidities [32].

Physical and physiological recovery after a period of critical illness is slow and often incomplete, therefore limiting the period of immobility and promoting movement and exercise are attractive strategies to prevent neuromuscular weakness and enhance recovery [32, 33, and 34]. Survivors from an acute respiratory failure have exercise limitation and decreased physical quality that can persist up to 5 years after hospital discharge. These patients find difficult to lift and carry groceries, climb stairs, bend, kneel, walking moderate distance and perform other routine activities of daily living [33]. Early mobilisation and exercise therapy within the ICU target the goals of enhancing the functional outcome, health-related quality of life and reducing of health-care utilization [16].

Wright et al studied if intensive (90 min) vs standard (30 min) physical rehabilitation therapy in critically ill patients after receiving 48 hours or more of either invasive or non-invasive ventilation added any benefit at 6-month time [34]. They found no difference in either the primary
outcome of self-reported physical health at 6 months, or the secondary outcomes like functional ability, independence, length of ICU and hospital stay [34]. Moss et al proposed a graduate manner to increase the physical training programme, for 30 min while in ICU up to 60 min when the patient was in a regular ward, in an outpatient setting or at home, with 5 components: techniques for proper breathing during exercise; progressive range of motion; therapeutic exercises addressed to the muscle strength; exercises designed to improve core mobility and strength; and functional mobility retraining including bed mobility, transfers, gait and balance [33]. Unfortunately, an intensive physical therapy programme did not improve long-term physical functioning compared with a standard-of-care physical therapy programme [33].

Airway clearance during chest infections through intensive physiotherapy consists in a modified active cycle of breathing technique accompanied by physical procedures such as percussions and shaking, and manually assisted cough; however, standard or intensive physiotherapy might be tiring for the patients and can precipitate episodic oxygen desaturation [35]. There are some cough augmentation techniques like: cough after inspiration supported by a NIV ventilator type BiPAP; exsufflation-assisted cough with delivery of negative pressure initiated manually at the end of inspiration; insufflation (given manually during inspiratory phase) and exsufflation-assisted cough with delivery of the negative pressure immediately preceding the cough effort via a facial mask [35]. Mechanical insufflation-exsufflation (MIE) technique is not an alternative for secretion clearance but can be vital for expelling secretions from central airways for patients with weak respiratory muscles and a partially preserved bulbar (laryngeal intrinsic) muscle function [36]. MIE is well tolerated and should be considered as an adjunct to manual airway clearance techniques for patients with a peak cough flow less than 160 L/min [8].

### 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 [37]. Therefore, NIV was proposed has 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 [19], with both improvement in physical functions and exercise performance [11]. 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 [38]. It is currently unknown if the demonstrated benefit of NIV during exercise training is clinically worthwhile or cost-effective [38].

NIV delivered during exercise enables patients with severe COPD to exercise at higher intensity, to increase their exercise endurance time and walking distance [8, 39]. NPPV is a feasible and beneficial tool in hospital-based PR [39], 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 [8, 40]. 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 [8, 39]. The benefits are achieved through optimization of the respiratory muscle load-capacity-drive relationship [8].

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 [41]. The pNIV device delivers 18 cmH2O inspiratory and 8 cmH2O expiratory pressures, and it is used only during recovery periods interspersing bouts of moderate or high-intensity physical activity [41]. 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 [41]. Future studies should investigate the additive effect of oxygen supplementation to intermittent NIV support during conventional PR [41].

Less practical in daily life but providing a greater improvement in exercise tolerance are the continuous positive pressure support devices like CPAP, inspiratory pressure support including proportional assist ventilation (PAV), and non-invasive “open” ventilation (NIOV) [15, 41, 37]. All these ventilation support strategies provide continuous unloading of the respiratory muscles and reduce the work of breathing [41], thus reducing dyspnoea and enhancing exercise tolerance in COPD patients [15]. Inspiratory pressure support strategies used during exercise increase endurance, reduce dyspnoea, unload the respiratory muscles, and sustain exercise induced lactatemia for longer [42, 37].

Portable CPAP devices, light-weighted and battery-powered, are particularly 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 [8]. 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 [37]. NIOV system, 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 [43].

They have been compared the effects of high-intensity training with mouthpiece inspiratory pressure support (IPS) delivering 10 cmH2O with 5 cmH2O. IPS10 resulted in significantly larger improvements in exercise endurance than training with IPS5 in moderate or high-intensity physical activity [37]. Therefore, it is suggested that IPS10 may be considered as adjunct during high-intensity training through better unloading the inspiratory muscles during exercise [44]. The authors found from experience that a mouthpiece is the most practical interface for the application of non-invasive ventilatory support during exercise, due to a reduced leakage of air compared with face masks and a better tolerance by the patients [44].

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 best 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 [19].

Negative pressure ventilation, when used as an adjunct 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 [10]. Maintenance of NPV reduces long-term mortality in COPD patients, irrespective of the presence of desaturation during the 6MWT. Huang et
al [22] initiated an unsupervised home endurance exercise programme and patients underwent once a week a comprehensive hospital-based PR programme where they received NPV via the cuirass ventilatory settings for 60 min. The authors have shown that NPV can improve the walking distance and reduce the yearly decline of lung function, exacerbations and hospitalization rates, and medical costs in patients with COPD during a 5-year observation [22]. It is speculated that reduction of lung function decline might be a consequence of NPV effects in improving ventilation pattern, arterial blood gas exchange and unloading of inspiratory muscles, thus reducing the work of breathing in COPD patients; conclusively, NPV may be used as an adjunctive therapy to PR [22]. Another benefit of NPV could be an improvement in clearance secretions and inflammation and decrease in AECOPD rate [22].

Recently, the same group of researchers have shown that a programme of maintenance NPV for COPD patients suggests that beneficial clinical effects are produced by decreasing dead space and inhomogeneous lung ventilation, increasing pulmonary perfusion and clearance of mucus plugging that is associated with lung atelectasis, thus leading to improved ventilation-perfusion mismatching and shunting, and reduced hypoxaemia at rest and during exercise [10]. The NPV programme 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 pursed-lipped, controlled and diaphragmatic breathing [22].

**At home**

After successfully completing a course of PR, the only way to maintain the achieved improvements is to continue with a home-based exercise programme and participate to follow-up visits in the PR centre. The scope is to make chronic respiratory patients to become more active in daily living life and to preserve endurance capacity, psychological and cognitive benefits [12]. NIV can be used for long-term treatment of chronic respiratory failure at home. High-pressure NIV is addressed to the patients who have persistent hypercapnia for 2 to 4 weeks after resolution of respiratory acidemia that has required acute NIV [24]. In COPD patients, long-term NIV decreases arterial partial pressure of carbon dioxide (PaCO2) and improves mortality [16]. Effective NIV, that significantly reduces elevated PaCO2 is well tolerated and associated with improvements of quality of life and long-term survival [11]. After 12 weeks of use at home the NIV devices, patients reported reduced anxiety and recovery time from breathlessness, as well as improvement in the speed, duration and confidence to undertake activities of daily living [41].

Another treatment option would be the use of NIV in addition to oxygen therapy in home setting, at least for 6 hours per day. Recent results of a randomized clinical trial published in 2017 support the use of home oxygen therapy and home mechanical ventilation (HOT-HMV) in COPD patients following acute life-threatening exacerbation of COPD, with acute respiratory failure and persistent hypercapnia. In HOT-HMV clinical trial, the addition of home NIV to home oxygen therapy has prolonged the time to readmission or death within 12 months from 1.4 to months to 4.3 months [24]. Patients with severe COPD receiving HMV can easily use NPPV during walking without changing ventilator settings or equipment [45]. When using only oxygen supplementation, arterial oxygen tension decreases during walking, but it increases when NPPV is used in addition to supplemental oxygen, with less dyspnoea and increased walking distance [45]. Moreover, NPPV used during exertion may prevent death from hypoxia-induced complications, especially arrhythmias [45].

**In palliative care services**

In advanced chronic patients admitted to palliative care services, it is essential to reduce breathlessness and improve survival, quality of life and function. The use of PAP devices in end-stage hypercapnic disease is frequently implemented in clinical practise, as suggested by international guidelines. Notably, timing of its initiation remains controversial because of potential side-effects as mask discomfort and limited communication with caregivers and family [8]. Although studies evaluating the effects of NIV over dyspnoea when used in palliative care settings are missing, prospective longitudinal studies have shown that hospital survival amongst patients with COPD and congestive cardiac failure with do-not-intubate order are unexpected high (30-60%) [8]. Moreover, their 3-month quality of life is equivalent to patients managed with acute NIV with no pre-set ceiling of care [8]. NPPV is a mean of potentially ensuring the highest quality of life during the final hours [29, 30], allowing to reduce the dose of morphine necessary to palliate dyspnoea, maintaining better cognitive function and with a similar rate of acceptance by patients compared with oxygen therapy [28]. The international guidelines suggest offering NIV to dyspnoeic patients for palliation in the setting of terminal cancer or other terminal conditions [28].

**Conclusions**

Pulmonary rehabilitation is a unique non-pharmacological therapy addressed to symptomatic COPD and non-COPD patients with a poor HRQoL due to breathlessness and fatigue. Because of dyspnoea, patients become more socially isolated and finally housebound. PR, LTOT and NIV bring hope in this difficult and long-term fight with a chronic respiratory disease, encouraging patients to meet other people with same disability and fear from illness and death, to exercise together and to continue their lives in a better condition. There is enough room, need and available technology to implement NIV worldwide, to encourage both patients and researchers to look ahead and find the best answers for the reported practical problems.

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