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REVIEW

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An update on pulmonary rehabilitation techniques for patients with chronic obstructive pulmonary disease

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ABSTRACT

Introduction: Pulmonary rehabilitation (PR) is one of the core components in the management of patients with chronic obstructive pulmonary disease (COPD). In order to achieve the maximal level of independence, autonomy, and functioning of the patient, targeted therapies and interventions based on the identification of physical, emotional and social traits need to be provided by a dedicated, interdisciplinary PR team.

Areas covered: The review discusses cardiopulmonary exercise testing in the selection of different modes of training modalities. Neuromuscular electrical stimulation as well as gait assessment and training are discussed as well as add-on therapies as oxygen, noninvasive ventilator support or endoscopic lung volume reduction in selected patients. The potentials of pulsed inhaled nitric oxide in patients with underlying pulmonary hypertension is explored as well as nutritional support. The impact of sleep quality on outcomes of PR is reviewed.

Expert opinion: Individualized, comprehensive intervention based on thorough assessment of physical, emotional, and social traits in COPD patients forms a continuous challenge for health-care professionals and PR organizations in order to dynamically implement and adapt these strategies based on dynamic, more optimal understanding of underlying pathophysiological mechanisms.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world and is the third leading cause of global disability-adjusted life-years (DALY) among non-communicable diseases [1]. Despite advances in pharmacological treatments, a large proportion of patients remains symptomatic and suffer from frequent exacerbations and hospitalizations.

In addition, concomitant chronic diseases occur frequently in COPD patients [2–4]. Physical inactivity is a well-recognized disadvantageous lifestyle factor, leading to a downward spiral which predisposes patients to an impaired health status, increased rates of hospitalization and mortality [5,6]. Thus, there is a clear clinical indication for additional, comprehensive interventions such as PR taking into account the individual's characteristics and comorbidities [1].

Already in the first authoritative statement, PR was introduced as an art of medical practice, wherein an individually tailored, multidisciplinary program is formulated through accurate diagnosis, therapy, emotional support, and education to stabilize or reverse both physiopathological and psychopathological manifestations of pulmonary diseases. Such a program must attempt to return the patient to the highest possible functional capacity allowed by the degree of lung function impairment and overall life situation [7].

More recently, PR has been defined as a comprehensive intervention based on a 'thorough' patient assessment followed by patient-tailored therapies designed to improve the physical and psychological condition of patients with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors [8]. Offering a patient-tailored, individualized, comprehensive intervention targeting complex needs to improve physiological, psychological and social outcomes and to promote long-term adherence to health-enhancing behaviors must be the cornerstone of every rehabilitation program [8–10]. PR programs are organized around the patient and his/her identified needs and traits.

The multifaceted manifestation of COPD and the individual patient characteristics make PR a complex health-care intervention, adaptable to the patient needs [11]. The current review focuses on developments and interventions to particularly tackle the physical manifestations of the disease. The review illustrates new developments beyond exercise training as dynamic developments within PR as a consequence of better insights in underlying pathophysiological manifestations contributing to the experienced individual burden of the disease.

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Article highlights

- COPD is a heterogeneous clinical syndrome. PR as comprehensive individualized intervention based on a thorough assessment of functional, emotional and social traits is a complex management strategy to implement.
- PR is a multifaceted, multidisciplinary management approach with individually tailored interventions requiring full understanding of mechanisms underlying patient's experienced disease burden.
- Improving functional performance as part of PR is more than exercise-based care and needs to integrate new innovative interventions based on profound pathophysiological insights into functional limitations.

2. Cardiopulmonary exercise testing and selection of training modalities

Exercise intolerance is a cardinal feature in COPD patients [12]. The underlying mechanisms vary in patients with similar resting ventilatory impairments [13]. There is growing recognition that the pathophysiological consequences of COPD are influenced by comorbidities. Indeed, cardiovascular diseases are highly prevalent in COPD, have an impact on patient's level of disability and quality of life [14–16], and contribute to reduced survival [17]. An accurate estimate of functional capacity by cardiopulmonary exercise testing can provide information about the influences of the cardiac, respiratory, musculoskeletal and hematological systems [18]. Such assessment of the integrated cardiopulmonary response to exercise remains largely underutilized in the personalized assessment and management of COPD patients with exercise limitation and breathlessness. Particularly in PR, field tests are applied in order to give an overall measurement of exercise capacity.

Among ventilatory inefficiency measurements, it has been reported that increases in the ventilation intercept in the $\dot{V}E/\dot{V}CO_2$ plot better express the progressive worsening on exercise ventilatory inefficiency across the continuum of COPD severity [19]. Also, this parameter is related to greater mechanical constraints, worsening pulmonary gas exchange, higher dyspnea scores and reduced exercise capacity [19]. This ventilatory inefficiency was already found in patients with mild airflow limitation, suggesting coexisting ventilation-perfusion abnormalities [19]. Heart failure (HF) with reduced left ventricular ejection fraction has discernible effects on selected physiological responses to exertion in patients with COPD: an unusually high ventilatory response to metabolic demand (low $\dot{V}E$-$\dot{V}CO_2$ intercept, high $\dot{V}E$-$\dot{V}CO_2$ slope and high peak $\dot{V}E/\dot{V}CO_2$ ratio) and low peak end-tidal partial pressure for CO_2 values, reflecting alveolar hyperventilation and/or lung perfusion abnormalities are more frequently reported in patients with both conditions than in those with COPD only [20].

In overlapping COPD-HF patients, in particular breathlessness and poor exercise tolerance seem strongly influenced by interpatient variability on respiratory centers' chemostimulation. Particularly, in the subgroup of patients with resting hypocapnia the excessive ventilation hastens dynamic abnormalities in pulmonary mechanics [21].

In COPD patients, the reported acute-on-chronic hyperinflation may result in a reduction in peripheral muscle blood flow due to the central hemodynamic consequences or cardiac output redistribution toward the overloaded respiratory muscles [22,23]. In heart failure, low cardiac output, global sympathetically mediated vasoconstriction and microvascular abnormalities characteristically compromise appendicular muscle blood flow [24]. Therefore, it can be expected that muscle blood flow impairment is markedly greater in COPD-HF overlap patients compared not only to COPD but also to HF patients [25].

Particularly, the presence of impaired aerobic function, indicated by a low $\Delta \dot{V}O_2/\Delta$ Work rate during incremental cardiopulmonary exercise testing, discriminates a subgroup of patients with COPD-HF who are particularly symptomatic and disabled. These abnormalities are associated with higher leg discomfort and breathlessness during rest and on exertion [26].

This profound pathophysiological understanding of the mechanisms underlying exercise intolerance may guide physicians toward a more personalized management strategy in COPD patients with different co-occurring conditions. Clinicians must consider maximizing lung deflation, particularly in the COPD-HF overlap group in order to attenuate the negative hemodynamic consequences of higher operating lung volumes in these patients [27]. Identification of the subgroup of COPD-HF patients with excessive exertional ventilation may guide rehabilitative interventions to select rehabilitative strategies with low-to-minimal ventilator stress [21]. Overlap patients seem particularly prone to respond to interventions that increase skeletal muscle O_2 delivery and/or reduce O_2 demand [25,26]. Unloading the respiratory muscles by noninvasive positive pressure ventilation can be considered as an option to improve muscle oxygenation during exercise [28]. Appropriate physical training strategies as one-sided lower-limb exercise training or neuromuscular electric stimulation (NMES) are options for very symptomatic patients with severe cardiorespiratory constraints [29–31].

3. Different modes of exercise training

Exercise training has been acknowledged as the cornerstone of a comprehensive PR program [8,32–34]. Eight to 10 weeks of exercise-based PR can lead to clinically relevant improvements in daily symptoms (dyspnea, fatigue, anxiety and/or depression), physical capacity, physical activity and quality of life in patients with COPD, without a significant change in the degree of airflow limitation [35–38]. Indeed, if exercise training is lacking, there is no significant improvement in exercise tolerance [39].

Most training studies focussed on the effects of whole-body endurance exercise training (i.e. treadmill walking and/or stationary cycling) [40]. Nevertheless, not all patients with COPD are able to exercise for a continuous period of 20 min or more at a training intensity of 60% or more of the predetermined maximal exercise tolerance [41,42]. Therefore, many other exercise training modalities and settings have been studied, ranging from Nordic walking for COPD patients with a relatively preserved exercise tolerance [43] to NMES for the most dyspneic, weakened and perhaps even mechanically ventilated patients with COPD [44]. Even though multiple training modalities and settings are available, a true personalization of the exercise training based on the pre-rehabilitation assessment is mostly lacking. A one-size-fits-all approach is common practice [34,40].

Reasoning from traits that are modifiable during exercise training, there are multiple options. Resistance training (training small muscle groups at 70–80% of the one repetition maximum (1RM), 4 sets of 8–12 repetitions) should be considered for patients with lower-limb muscle weakness/atrophy and a moderate degree of dyspnea (mMRC 2) [45,46]. For weakened COPD patients with (very) severe dyspnea, resistance training may still be too burdensome to the impaired ventilator system [47,48], and NMES should be considered as a substitute for resistance training [49]. Whole-body vibration has also been suggested as a useful mean to increase lower-limb muscle strength [50] but seems not be used very often in daily clinical rehabilitation practice [51].

Whole-body exercise training can be considered for patients with a clear exercise intolerance. Patients who are mainly restricted by reaching their maximal heart rate during the cardiopulmonary exercise test, should be offered whole-body exercise training (at 60% to 80% of the pre-determined maximal cycling load/walking speed, for 20–30 min), which can range from treadmill walking to stationary cycling, and outdoor walking, including Nordic walking [8,43]. Patients who are mainly restricted by the ventilatory system, should undergo a constant work rate cycling endurance test (CWRT) at 75% of the peak cycling load. If the CWRT lasts ≥10 min, endurance training (starting at 60%) is still an option. If the CWRT lasts <10 min, interval training (at >80% of the pre-determined maximal cycling load/walking speed, for 30–60 s per exercise bout, for 20 to 40 bouts) using treadmill walking or stationary cycling should be proposed. Interestingly, patients who cycle <10 min also have weaker quadriceps muscle [52]. In turn, interval training should most probably be combined with resistance training. Obviously, the rehabilitation goals of the patient should be taken into the equation, as interval training matches to a greater extent the metabolic load of activities of daily living than endurance training [53,54]. If there are clear signs of exercise-induced oxygen-desaturation during the cardiopulmonary exercise test [55,56], the rehabilitation team may want to consider the use of oxygen supplementation during the whole-body exercise training, although its use has been questioned recently. Indeed, Alison and colleagues showed that a 10-week exercise training program was safe and effective in patients with COPD with mild exercise-induced O2-desaturation who were training with oxygen supplementation or room air supplementation [57].

To prevent exercise-induced oxygen-desaturation, again, interval training should be considered. Moreover, patients with severely exercise-induced lung hyperinflation may be in need of ventilatory support during whole-body interval training. This can be provided using noninvasive ventilation [58–60]. This requires a lower physiotherapist–patient ratio compared to ‘regular’ supervision of exercise training, which may be an organizational challenge. Obviously, the first step here is to teach patients to use pursed-lips breathing, which may partly prevent dynamic lung hyperinflation [61]. Besides stationary biking (instead of treadmill walking), water-based walking seems also a valid option for COPD patients with obesity and/or arthrosis of hip/knee/lower back [62].

To date, exercise training generally results in an improved exercise tolerance in patients with COPD and two-thirds of the patients achieve a clinically relevant improvement in physical capacity [38,63]. Whether a further personalization of the exercise training intervention(s) as part of a comprehensive PR program will improve these numbers remains to be determined.

4. Neuromuscular electrical stimulation in patients with COPD

Patients with COPD, who are mostly characterized by ventilatory limitation, are not always able to train at a sufficient intensity during endurance training due to exercise-induced dyspnea [41]. For this reason, there is interest in interventions, which provide an optimal training load in these severely dyspneic patients in a PR program. Transcutaneous NMES may be such a suitable rehabilitative option, which can be delivered by a portable stimulator. The ventilatory load and symptom scores for dyspnea have been shown to be low over time with increasing training loads of NMES in patients with COPD [47]. Moreover, COPD patients with increased dyspnea scores are less likely to complete a PR program [64]. NMES has been shown to be an effective training modality in COPD patients who are hospitalized because of a severe exacerbation [65–67]. Therefore, for dyspneic patients with COPD with muscle weakness, NMES may be an effective alternative rehabilitative modality [68].

NMES involves the application of a series of intermittent stimuli (stimulation-rest cycles) with the aid of percutaneous electrodes over superficial skeletal muscles, with the main objective to trigger visible muscle contractions due to the activation of the intramuscular nerve branches [69–71]. There are several differences in the muscle contractions, elicited by the normal biological pathway or by electrical stimulation. The activation order of motor units is different from the physiological recruitment pattern according to the size principle [72]. Contradictory findings on motor unit recruitment order have been found [70]. Some studies suggest preferential or selective activation of fast motor units with NMES [73,74], whereas others suggest that motor unit recruitment during NMES reflects a nonselective, spatially fixed, and temporally synchronous pattern rather than in a reversal of the physiological voluntary recruitment order [75]. These diverse results could have been related to differences in protocols and stimulated muscles [71]. Another difference with voluntary contractions is that NMES activates the muscle to a greater extent under identical technical conditions [76]. At identical levels of workload (10% of the quadriceps maximum isometric voluntary torque), the muscle reaches higher values in blood flow and oxygen consumption during NMES compared with voluntary contractions [76]. NMES training sessions generally last 10–30 min during a 4- to 5-week period that involves 20–25 sessions to increase peripheral muscle function [71]. A pulse duration of at least 300 μs is recommended to stimulate large muscle groups such as the mm quadriceps femoris [77]. Two types of NMES frequencies can be distinguished: high-frequency NMES (HF-NMES, ≥50 Hz); and low-frequency NMES (LF-NMES, <50 Hz) [70,71,77,78]. Frequencies of 50 Hz and above induce a fused tetanus [79,80] and generate higher torques than low frequencies [81]. The DICES trial showed that peak muscle strength increased with supervised NMES sessions twice per day following 75 Hz but not following 15 Hz during a PR program of 8 weeks [49]. Functional exercise performance, problematic activities of daily life, mood status, and health status improved significantly following both frequencies [49].

In 2018, Hill and colleagues conducted a Cochrane review in which 16 studies incorporating 267 patients with COPD were included [82]. Seven studies analyzed the effects of NMES versus usual care and nine studies analyzed the effects of NMES combined with regular exercise training versus exercise training alone. The findings were that NMES in isolation versus usual care increased quadriceps function (strength and endurance), functional exercise performance and reduced the severity of leg fatigue. They also concluded that there were no additional effects in quadriceps strength of NMES on top of regular exercise training, but functional exercise performance increased [82]. However, in this review, no distinction has been made in patients who are capable of regular exercise training like endurance training and patients who were hospitalized because of an acute exacerbation [82]. In patients who are able to perform voluntary exercise training the combination with NMES is hardly of added value [83]. However, in patients who are hospitalized, the combination of NMES and active mobilization led to improvements in muscle strength, dyspnea, exercise performance and the amount of days to make the transfer from bed to chair [84,85].

NMES devices differ a lot in costs, sufficient portable devices cost circa 600 euro and are available in shops for physical therapy or rehabilitation. Session times of NMES differ between 15 and 30 min. It is possible to train more patients in a group, if more devices are available.

In conclusion, NMES is recommended in patients with COPD who are not capable of regular exercise training such as endurance training because of an acute exacerbation or exercise-induced dyspnea. Also, if patients are not capable of cycling or treadmill training due to orthopedic problems, NMES may also be a suitable training modality [86].

5. Training, oxygen and noninvasive ventilatory support

Development of hypoxia and dynamic hyperinflation (DH) are two of the most important factors resulting in early termination of exercise [8,87,88] and may limit the capacity of patients to engage in exercise training of sufficient intensity. Supplementation of oxygen and/or noninvasive ventilatory support may enhance the effects of PR in those with severe disease.

Disturbances in gas exchange can occur due to airflow limitation, destruction of lung parenchyma and/or pulmonary vascular bed abnormalities in patients with COPD. Patients who receive long-term oxygen therapy according to international guidelines should have this continued during exercise training, but it is generally advised to increase flow rates as oxygen demand increases during exercise [8]. Results on the impact of oxygen supplementation during exercise in COPD patients with exercise-induced desaturation (EID) but normoxemia at rest are equivocal. Oxygen supplementation during exercise can improve endurance time and reduce dyspnea in COPD patients with mild hypoxemia or EID, by slowing down the respiratory rate and thereby the lowering the degree of exercise-induced DH [89–93]. However, Rooijackers et al.[94] reported no additional effect of training with supplemental oxygen on exercise performance or health status compared to training with room air in patients with EID. Also, Garrod et al.[95] showed no benefits of training with supplemental oxygen compared to room air in patients with EID regarding exercise tolerance or health status. Very recently, a large double-blinded RCT showed that supplemental oxygen used during an 8-week supervised exercise training program in normoxemic COPD patients with EID did not result in greater improvements in exercise capacity than did medical air [57]. This was a large prospective-blinded study, but the investigators did not evaluate the acute response to oxygen supplementation. Indeed, it was previously shown that a positive acute exercise response to oxygen may be used as a selection criterion for patients that may benefit from training with supplemental oxygen [96].

Recent guidelines recommend the use of nocturnal noninvasive ventilation (NIV) in patients with chronic hypercapnic respiratory failure (CHRF) with nocturnal P_aCO_2 values ≥ 55 mmHg [97], as it has been shown to significantly reduce hypercapnia, time to hospital readmission and mortality risk [98,99]. Additional nocturnal NIV during PR in COPD patients with CHRF can result in improved health-related quality of life, dyspnea and exercise tolerance [100]. NIV can reduce the load of the overburdened inspiratory muscles and the work of breathing [101], and thereby reducing hypercapnia and dyspnea [102]. Unloading the respiratory muscles prevents exercise-induced diaphragmatic fatigue and improves leg muscle oxygenation [103,104]. Also, DH might be reduced or delayed [105]. However, the role of NIV as an add-on intervention during exercise training remains to be established.

To date, only a few studies have investigated the short- and long-term effects of NIV during exercise, with partially promising but inconsistent results [102,106]. Higher pressures (inspiratory pressure support >20 cm H_2O) seem to be more effective, and normocapnic patients are less likely to have beneficial effects from NIV during exercise. Indeed, patients with severe physical impairment but without hypercapnia do not have an indication for NIV during exercise [97], and also seem able to perform exercise training without NIV [107]. However, CHRF patients with end-stage lung disease may not be able to perform effective exercise training at all without the use of NIV. A recently published study with 20 COPD patients with CHRF investigated the differences in exercise duration using oxygen with or without high-pressure NIV. NIV in addition to oxygen significantly improved P_aCO_2 levels, dyspnea and endurance time [108]. The use of NIV during exercise requires expensive technical equipment and qualified staff. With this in mind, along with the current evidence available, NIV as an add-on tool during exercise should be reserved for highly selected patients with chronic hypercapnic respiratory failure.

6. Pulsed inhaled nitric oxide and rehabilitation in COPD patients with pulmonary hypertension

An estimated 30% to 70% of patients with COPD also has pulmonary hypertension (PH) [109]. The prognosis is particularly poor in COPD patients with severe PH and a resting PAP >35–40 mm Hg [110,111]. Inhalation of nitric oxide (NO) with oxygen could be a promising treatment in patients with COPD and PH. NO is an important mediator in vascular reactions especially in pulmonary circulation. Oral compounds can act by NO mediated pathways, but delivering pulsed inhaled NO (iNO) directly to the airways and pulmonary vasculature could results in additional patient benefits [112]. Inhaled NO produces pulmonary vasodilation with minimal effect on systemic vascular beds due to its high affinity for hemoglobin and rapid inactivation. A NO pulsed system gives a small concentration of NO at the beginning of the inspiration. Advantage of delivering in pulsed doses early in inspiration is that it delivers the drug selectively to the healthiest lung segments by using a short pulse width.

The relevance of vasodilation induced by pulsed iNO treatment is demonstrated in PH-COPD patients on long-term oxygen therapy (LTOT) assessed by Functional respiratory imaging (FRI). All patients experienced acute increases in blood vessel volumes following iNO treatment (+4.2%, $p = 0.03$). There was a significant association ($p < 0.01$) between ventilation and vasodilation during iNO therapy, suggesting that regions with better ventilation experience more vasodilation. The patients who completed 4 weeks of iNO therapy-experienced reductions in pulmonary arterial pressure (−19.9%, $p = 0.02$) and had a 50.7 ± 54.4 m increase in 6-min walk distance ($p = 0.04$) [113]. In addition, patients reported improvement in shortness of breath at rest and with exercise. Chronic iNO therapy has the potential to significantly increase exercise tolerance and shortness of breath in COPD patients with PH. Chronic iNO therapy has the potential to become an add-on intervention strategy as part of an integrated rehabilitation program in these patients.

7. Lung volume reduction and pulmonary rehabilitation

The emphysematous COPD phenotype is histopathological characterized by enlargement of the air spaces distal to the terminal bronchiole with destruction of the alveoli. The elasticity of emphysematous lungs is reduced. This leads to hyperinflation as a result of premature closure of small airways during expiration (air trapping), together with the natural outward force of the chest wall which overcomes the inward force of elastic lung recoil [88]. Hyperinflation impairs respiratory muscle mechanics, negatively affects cardiac function, decreases exercise performance and is associated with increased mortality [114,115]. Of particular importance is the exercise-related increase in hyperinflation in patients who are already hyperinflated at rest. Due to insufficient time to deflate the lungs with increasing breathing frequency during exercise: this condition is commonly described as dynamic hyperinflation. Static and dynamic hyperinflation have major implications for dyspnea and exercise limitation, and hence PR programs [88,116].

The limited ventilatory reserve in these patients, restricts to a great extent the possibilities of endurance training in these patients. Lung volume reduction techniques are introduced to create breathing reserve for these patients, and the newly improved breathing mechanics could be synergistically used to improve outcomes of PR.

Nevertheless, it has been repeatedly shown that PR programs can be successful implemented even in severely hyperinflated patients, and could help to identify the right candidates for these resources.

In 2011, Crisafulli et al.[117] retrospectively evaluated the effect of PR on exercise tolerance in patients with hyperinflation. The hyperinflation group, with a mean residual volume of 180% predicted, showed a 72-meter improvement on the six-minute walking test (6MWT) post rehabilitation. The authors concluded that PR in COPD patients characterized by hyperinflation is beneficial to patient outcomes. A limitation of this study was that hyperinflation was solely based upon body plethysmography measurements without radiologic images confirming emphysema.

Vanfleteren et al.[118] evaluated retrospectively the effect of PR in patients with different degrees of hyperinflation. As hyperinflation increased, patients were more prone to cachexia, were of younger age and had worse exercise capacity. All patients, irrespective of the severity of hyperinflation, showed improvement on exercise capacity and quality of life [118].

In the pivotal, multi-center, randomized National Emphysema Treatment Trial (NETT) patients completed a pre-operative 6 to 8 week PR program before randomization between lung volume reduction surgery (LVRS) versus optimal medical treatment [119]. Patients who fulfilled the pre-operative PR program improved in exercise capacity and quality of life while dyspnea decreased [120]. Indeed, a number of patients were not deemed eligible after PR as they improved in such extent that surgery was no longer applicable. In addition, post-hoc analysis of the NETT trial, showed that the best response of LVRS was seen in the subgroup of patients with persistent low exercise capacity after PR. Hence, PR is an important tool to properly select the patients most likely to benefit from LVRS [120].

While PR has consistently been shown to be effective in COPD patients to improve exercise capacity and reduce breathlessness [40], it has little effect on ventilatory limitation. Therefore, interventions targeting hyperinflation warrant further investigation. Of notice, Casaburi et al. showed in a placebo-controlled study that receiving tiotropium in combination with PR resulted in significantly longer exercise endurance time compared to patients in the control group [121]. Tiotropium has been shown to decreases hyperinflation over 24 h and improve continuous work rate endurance on cycle ergometry [122]. Recently, it was shown that dual bronchodilatation improves exercise capacity in patients with COPD participating in a self-management behavior-modification program, irrespective of add-on exercise training [123], emphasizing the importance of lung deflation.

More recently, less invasive bronchoscopic alternatives have become available as an alternative for surgery, which was more and more abandoned due to high risk of complications, morbidity, and mortality [124]. Bronchoscopic lung volume reduction (BLVR) using one-way valves, successfully reduces thoracic gas volume and leads to significant improvements in lung function, exercise capacity and quality of life [119,125,126] in emphysematous COPD patients characterized with sever hyperinflation.

Lung volume reduction aims to reduce end-expiratory long volume (EELV) which adds a mechanical advantage to the respiratory muscles by setting the length–tension relation at a more beneficial position and thereby restoring their force-generating capacity [127]. Moreover, volume reduction lessens elastic recoil and by increasing the inspiratory capacity it allows more tidal volume expansion which is necessary during exercise [128]. Patients may be able to exercise longer or with a higher intensity, thereby inducing an improved physiologic training effect on the muscles. This may generate better results in exercise tolerance. Patients may engage in daily activities for longer periods of time, which may also contribute to benefits observed from formal exercise training. Furthermore, gained benefits may have a longer-lasting effect due to the higher exercise tolerance attained.

However, the majority of trials investigating specific interventions in lung volume reduction focused on patients who had undergone a form of exercise training before treatment. The effect of the timing of PR, pre or post lung volume reduction intervention, has never been studied. Reducing hyperinflation beforehand could potentially lead to longer exercise time and/or greater intensity and as a result strengthen the effect of PR.

A prospective randomized study is currently ongoing to address the optimal timing of PR in patients with advanced emphysema eligible for BLVR [129].

8. Gait assessment and training

Patients with COPD report walking (gait) as one of the most problematic activity in daily life [130]. Indeed, they walk less in daily life [131] and achieve shorter walk distances during the 6-min walk test (6MWT) as compared to healthy subjects [132]. Gait assessment could provide insight into factors associated with the reduced walk distances in patients with COPD.

To date, several studies have explored gait in COPD [132–136]. One study reported that gait alterations, such as limping and shuffling, are associated with disease severity in COPD [137]. Patients with COPD also demonstrate decreased cadence, shorter step lengths, increased time spent in double support and a lack of increase in peak ankle dorsiflexion moment after the onset of breathlessness or leg tiredness as compared to healthy subjects, while walking at their comfortable speed [133–135]. Balance disturbances in a mediolateral direction in patients with COPD were found during the 6MWT [132]. Furthermore, patients with COPD walk with increased step time variability and smaller step width variability during fixed speed treadmill walking [136].

Gait analysis could be conducted using various instruments including accelerometry [132], a pressure-sensitive mat [133], two-dimensional video recordings [134] and three-dimensional motion capture systems [135]. Accelerometry devices determine the quantity and intensity of movements and are widely available for clinical practice. These devices are less costly and time consuming then technology more advanced instruments such as three-dimensional motion capture systems. With increasing use of these advanced instruments, the more important it is to combine efforts of professionals from different fields such as health and biomechanics by sharing their experiences and skills and creating conditions for the development of new methods to improve patients' health. Gait analysis using instrumented treadmills require less laboratory space and may therefore be an alternative to overground gait assessment [138]. In addition, traditional treadmills impose limits to walking speed, resulting in less natural stride variability. Self-paced treadmill walking, involving a feedback-regulated treadmill that allows subjects to walk at their preferred speed, is suggested to be a suitable alternative to fixed speed treadmill walking in gait analysis [138]. Self-paced treadmill walking combined with a three-dimensional motion capture system could overcome the limitations in overground and fixed speed treadmill walking. Previous studies observed similar spatiotemporal, kinetic and kinematic gait characteristics in self-paced and fixed speed treadmill walking using such motion capture systems [138,139]. Moreover, gait speed in a self-paced treadmill was comparable to overground walking when using such a system [140]. These novel techniques enable accurate assessment of gait characteristics in patients with COPD within a safe environment. Therefore, it is important to select the optimal measure for use in patients with COPD, while taking into account the time, cost and availability of equipment and knowledge in clinical practice.

Recent studies have demonstrated the possible clinical implications of gait assessment in a clinical setting [141–143]. Patients with COPD are able to perform the 6MWT using a self-paced treadmill walking combined with a three-dimensional motion capture system with minimal differences compared to the overground 6MWT [141]. Patients with COPD demonstrate gait alterations during the self-paced treadmill-based 6MWT as compared to non-COPD subjects. In addition, a comprehensive PR program seems to affect gait characteristics in patients with COPD. Patients demonstrated faster mean stride times after PR. However, gait variability measures that are associated with falls, did not change following PR. Moreover, good responders, defined as those improving their GRAIL-based 6MWT of ≥30 m after PR, showed improvements in stride time and stride length as compared to poor responders (<30 m improvement after PR) [142].

Studies on gait characteristics in COPD is a field that needs to be explored in more detail. Changes in gait characteristics have been related to increased risk of falling in older adults [144]. As patients with COPD demonstrate balance impairment [145] and have a higher fall incidence [146], the relationship between balance impairments, falls and gait should be investigated in future studies. Gait assessment may be a promising tool for clinical purposes (e.g. diagnostics and evaluation after PR). Future training programs specifically targeting gait function may be considered as part of an integrated training program to improve gait characteristics in patients with COPD.

9. Nutritional support and PR

Abnormalities in body weight and/or fat-free mass (FFM) are common extra-pulmonary features in patients with COPD and their presence and clinical impact have been recognized for decades. Low body mass index (BMI) is associated with reduced exercise capacity [147] and increased mortality risk in patients with stable disease [148] as well as those hospitalized with exacerbations [149]. Irrespective of BMI, low FFM is commonly present in COPD and is associated with reduced skeletal muscle strength [150], exercise intolerance [151] and poor health status [152]. Moreover, FFM was identified as an independent predictor of mortality, irrespective of fat mass [153]. Over the last decade, there is increasing focus on the clinical implications of obesity in

COPD [154]. Obese patients are more symptomatic [155] and have reduced functional exercise capacity [156] than patients with a comparable degree of airflow limitation but with a normal weight. In patients with severe disease, obesity is associated with increased survival, a phenomenon referred to as the *obesity paradox* in COPD [148]. Also, nutritional status is an important discriminating factor in unbiased clustering of COPD patients. In overweight and/or obese patients, cardiovascular and metabolic comorbidities are more common [157], while COPD patients with underweight are more frequently characterized by low FFM and osteoporosis and emphysematous lung abnormalities [2].

Since nutritional status is considered one of the treatable traits of COPD, assessment of body weight and FFM is clinically relevant and recommended by international standards [158]. Bio-electrical impedance analysis is a noninvasive, easily applicable, safe, inexpensive and practical method to assess FFM in clinical practice [159], although dual-energy X-ray absorptiometry (DEXA) is most appropriate for combined screening of osteoporosis, FFM and fat mass [158]. Following nutritional assessment, nutritional counseling and supplementation may be incorporated in a comprehensive and individualized pulmonary PR program [8]. Several studies investigated the impact of nutritional support on body composition, muscle function, exercise capacity, health status and mortality in COPD. Ferreira et al. [160] performed a meta-analysis of studies with at least 2-week duration of nutritional interventions. Significant weight gain in favor of nutritional supplementation compared to placebo was reported in the total COPD population, although there was no significant difference in final weight between those who received supplementation and those who did not [160]. In underweight COPD patients, both more pronounced weight gain as well as increased post-intervention body weight were reported with nutritional supplementation compared to placebo [160]. In contrast to adequately nourished patients, a significant increase in FFM with nutritional supplementation was reported in the underweight COPD group [160]. Functional exercise capacity, muscle strength, and health status also significantly improved after nutritional supplementation [160]. The interpretation of this meta-analysis is hampered by large variability between studies that were included; nutrition with or without exercise training, outpatient versus inpatient setting, patients with abnormal versus normal nutritional status [160]. Studies that included exercise training reported larger gains in body weight compared to those that did not, while most pronounced changes in body weight were observed in studies that combined nutritional supplementation and exercise training in malnourished patients [160].

In order to enhance the benefits of exercise training and/or nutritional support, the effects of anabolic steroids have been investigated in COPD, mainly in male patients. Although significant increases in FFM have been reported [161–164], no consistent increases in muscle strength, exercise capacity or other relevant outcomes have been observed. Thus, anabolic steroids are not routinely used in the management of undernutrition in COPD.

No clinical trials investigated the effects of weight loss program for obese COPD patients. However, a combination of a 12-week weight reduction program involving meal replacements, dietary counseling and resistance exercise training resulted in significant weight loss and improved exercise capacity and health status [165]. Also, it was shown that obese patients benefit from PR to the same extent as non-obese COPD patients [166].

10. Sleep quality and pulmonary rehabilitation

Beyond common knowledge that sleep deprivation has negative effects on cognitive and physical performance as well as mood, it has been shown to be associated with adverse health outcomes. These include an impaired immune function, obesity, diabetes, hypertension, heart diseases, stroke as well as increased pain and depression, an elevated risk of accidents and an increased mortality [167]. Sleep duration of less than 5 h is associated with an almost fourfold mortality risk [168].

Disturbed sleep is frequently found in hospitalized patients in general [169] as well as specifically in patients suffering from various disorders including COPD. Insomnia is commonly found in these patients with prevalence values ranging from about 33% to above 70% [170–174]. Polysomnographic evaluation of sleep in patients with COPD demonstrates increased values for sleep latency, wakefulness after sleep onset as well as reduced values for total sleep time, sleep efficiency, and the amount of REM sleep and deep sleep [175]. The underlying causes of sleep disturbances in patients with COPD are diverse, including disease-specific risk factors, such as the severity of COPD [176,177], symptoms [178–180] and hypoxemia and hypoventilation [98,99,170,181–183]. Comorbidities such as depression and anxiety [2,184] as well as a cardiovascular disease may also contribute to sleep disturbances. Finally, primary sleep disorders such as the restless legs syndrome, primary insomnia, and obstructive sleep apnea may present as difficulty initiating and maintaining sleep. Recently, increased prevalence of OSA among COPD patients have been reported [185–187].

In a recent retrospective, cross-sectional study of 932 patients with COPD, in whom sleep and physical activity were evaluated using an activity monitor, patients across all GOLD stages showed reduced nocturnal sleep as well as reduced sleep efficiency. Sleep efficiency was most markedly and significantly reduced and sleep fragmentation was significantly increased in patients with the worst airflow limitation and the highest dyspnea scores. Importantly, there was a clear correlation between quality of sleep and physical activity. While a casual relation could obviously not be proven, it was however suggested by the fact that days with reduced physical activity were preceded by nights with poor sleep quality [188]. The underlying causes though, remain unclear, with increased work of breathing, associated symptoms or associated hypoxemia (see below) being potential candidates.

During rehabilitation for COPD (and many other diseases) however, patients are required to be alert in order to actively participate in educational, mental and physical activities of the program. Sleep disorders and sleep deprivation are counterproductive to this end.

The basis of insomnia treatment in COPD is optimal COPD management and control of nighttime symptoms. Inhaled bronchodilators may improve nighttime symptoms, but the results so far are conflicting and very few studies have targeted this problem. Abstaining from smoking can improve insomnia. In case of nicotine withdrawal, insomnia may initially worsen.

If case history taking reveals treatment targets such as e.g. anxiety/depression or restless legs, these should obviously be addressed. Treatment may include cognitive behavioral therapy for insomnia (CGT-i). Pharmacological hypnotic treatment can also be considered in short-time insomnia disorder, however caution and if possible intermittent use is advisable due to the potential of respiratory depression or aggravation of OSA. This applies particularly but not only to benzodiazepines [189–193].

Where OSA is the predominant component continuous positive airway pressure (CPAP) should be applied. Effective treatment with CPAP is associated with improved survival and decreased hospitalizations [194].

Exercise itself has been shown to improve sleep. Several mechanisms have been suggested such as thermogenetic effects, reduction of anxiety and depression and improvement of OSA [195–197]. In the presence of OSA, improvement with exercise has repeatedly been reported even without improving BMI. Rostral fluid shift from the lower body, improvement in upper airway function and improvement of body composition have been suggested as causal factors [198].

But not only exercise, PR too, even without specifically addressing sleep problems, may also serve as a non-pharmacological treatment to improve sleep in patients with COPD. Soler, Diaz-Piedra, and Ries [199] investigated the effects of an 8-week PR program (without sleep specific interventions) on sleep quality in 64 patients with chronic lung disease, 58 of which reported poor sleep quality at baseline. They found an improvement of sleep quality by 19% at the end of the program. Sleep was improved in the COPD group only. Similarly, Lan et al.[200] found an average improvement of the sleep quality index by 17% in 34 COPD patients after 12 weeks of PR.

The reasons underlying this improvement are not fully understood and may well be complex, involving physiological as well as psychological benefits from rehabilitation. Lessening of anxiety and depression, reduction of dynamic hyperinflation, reduction of systemic inflammation and improvement of OSA have been suggested as contributing factors [199,200].

Creating more awareness of sleep-related problems seems very relevant to improve patient outcomes in patients admitted for PR.

11. Conclusions

Patients with COPD may suffer from multiple physical, emotional and social features necessitating a comprehensive, individualized intervention offered as a personalized PR program. Taking this disease complexity and severity into consideration, PR must integrate the translation of knowledge and evidence of identified features into a multifaceted, complex intervention in order to deliver optimal PR. In this way, PR will strengthen the individual autonomy of the patient and offer the patient a maximal level of autonomy and functioning in the community.

12. Expert opinion

PR is defined as a comprehensive intervention targeting complex needs in patients with chronic respiratory conditions to sustainably improve physical, psychological and social outcomes. PR is a complex, individualized health-care intervention. Although exercise training has been acknowledged as the cornerstone of a comprehensive PR program, different flavors of training must be considered based on a profound pathophysiological understanding of the mechanisms underlying exercise tolerance particularly in COPD patients. Cardiopulmonary exercise testing can provide accurate information about the functional capacity of the cardiorespiratory system. Such assessment of the integrated response cardiopulmonary response to exercise can be very helpful in the personalized assessment and management of COPD patients with exercise limitation and breathlessness and to select appropriate rehabilitative strategies in particular in the group of symptomatic patients with severe cardiorespiratory constraints. Different intervention strategies are discussed in more detail: neuromuscular electrical stimulation (NMES), supplementation of oxygen and noninvasive ventilation, pulsed nitric oxide to attenuate pulmonary hypertension as well as the possibilities of lung volume reduction and PR. NMES is a good example how with the aid of percutaneous electrodes over superficial skeletal muscles, positive outcomes can be achieved even in those patients not capable of regular exercise training because of exacerbations or severe exercise-induced dyspnea. Some patients report walking as one of the most problematic activities. Patients with COPD demonstrate manifested gait alterations and PR affects these gait characteristics with improvements in stride time and stride length. The impact of abnormalities in body weight and muscle mass is now well recognized and the outcomes of nutritional intervention strategies as part of a comprehensive PR are reviewed. Otherwise, obesity particularly in combination with sarcopenia remains a challenge and more studies are needed how to tackle these metabolic abnormalities.

Disturbed sleep is largely neglected in the assessment of patients referred for PR: reduced nocturnal sleep as well as reduced sleep efficiency seem to be very relevant to improve outcomes of PR. Creating more awareness of sleep-related problems seems very relevant to improve outcomes of PR.

This review illustrates how PR dynamically integrates and translates a better understanding of disease complexity and heterogeneity into a multifaceted, complex and individualized intervention in order to offer optimal patient benefits. Based on a comprehensive assessment at the start of the program, physical, emotional, and social traits can be identified. Using targeted therapies, these traits can be addressed by a dedicated, interdisciplinary pulmonary team. The current review describes ongoing developments to tackle physical components of the disease, but the impact of multimorbidity, mental components as anxiety and depression as well as neurocognitive dysfunctioning can not be neglected and requires similar individualized strategies. These and other developments illustrate the experienced challenges for clinicians and health-care professionals to better understand underlying traits and the organizational complexity to implement dynamically these modalities in order to achieve the best outcomes even in disabled patients. These comprehensive, individualized interventions resulting from a thorough assessment of the patient differ from exercise-based care offered in home-based programs.

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